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Ambient Water Quality Criteria for Acrylonitrile

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Acrylonitrile. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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AMBIENT WATER QUALITY CRITERIA FOR
ACRYLONITRILE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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CRITERIA DOCUMENT

ACRYLONITRILE

CRITERIA

Aquatic Life

The available data for acrylonitrile indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 7,550 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No definitive data are available concerning the chronic toxicity of acrylonitrile to sensitive freshwater aquatic life but mortality occurs at concentrations as low as 2,600 µg/l with a fish species exposed for 30 days.

Only one saltwater species has been tested with acrylonitrile and no statement can be made concerning acute or chronic toxicity.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of acrylonitrile through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 0.58 µg/l, 0.058 µg/l, and 0.006 µg/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 6.5 µg/l, 0.65 µg/l, and 0.065 µg/l, respectively.

INTRODUCTION

Acrylonitrile is an explosive, flammable liquid having a normal boiling point of 77°C and a vapor pressure of 80 torr (20°C). The toxic effects of acrylonitrile are similar to cyanide poisoning although not identical. The chemical structure of acrylonitrile, $CH_2 = CHCN$, resembles that of vinyl chloride, a material known to cause human cancer.

At present 1.6 billion pounds of acrylonitrile per year are manufactured in the United States. The major use of acrylonitrile is the manufacture of copolymers for the production of acrylic and modacryclic fibers by copolymerization with methyl acrylate, methyl methacrylate, vinyl acetate, vinyl chloride, or vinylidene chloride [National Institute for Occupational Safety and Health (NIOSH), 1977]. Other major uses of acrylonitrile include the manufacture of acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins (used to produce a variety of plastic products), nitrile elastomers and latexes, and other chemicals (e.g., adiponitrile, acrylamide). Acrylonitrile has been used as a fumigant; however, all U.S. registrations for this use were voluntarily withdrawn as of August 8, 1978 (43 FR 35099). The U.S. Food and Drug Administration has recently banned the use of an acrylonitrile resin for soft drink bottles (Anonymous, 1977, 1978), but its use is still allowed in other food packaging. NIOSH estimates that 125,000 persons are potentially exposed to acrylonitrile in the workplace (NIOSH, 1977).

At present the body of evidence produced in both toxicity studies on laboratory animals and occupational epidemiologic studies on man suggests that acrylonitrile may be a human carcinogenic. Thus, NIOSH has recently stated that "acrylonitrile must be handled in the workplace as a suspect human carcinogen" (NIOSH, 1978). This judgment of NIOSH is based primarily on (1) a preliminary epidemiologic study of E.I. du Pont de Nemours and Co., Inc. on acrylonitrile polymerization workers from one particular textile fibers plant (Camden, S.C.); in this study, it was ascertained that a substantial excess risk (twice that expected) of lung and colon cancers occurred between 1969 and 1975 in a cohort exposed between 1950 and 1955 (O'Berg, 1979); (2) interim results from ongoing 2-year studies on laboratory rats performed by the Dow Chemical Co., and reported by the Manufacturing Chemists Association (April, 1977) (43 FR 192 45764) in which, by either drinking water (Quast, et al. 1980) or inhalation routes (Maltoni, et al. 1977) of acrylonitrile exposure, laboratory rats developed CNS tumors and Zymbal's gland carcinomas, not evident in control animals.

Aside from suggestive evidence of carcinogenicity in man and the experimental evidence in animals, numerous workers have reported on the other genotoxic charactistics of acrylonitrile (embryotoxicity, mutagenicity, and teratogenicity) in laboratory animals (Venitt, et al. 1977; Milvey and Wolff, 1977; Murray, et al. 1976). Even though there is some controversy over the chronic effects of acrylonitrile (Shaffer, 1975), the acute toxicity of acrylonitrile is well known, and the compound appears to exert part of its toxic effect through the release of inorganic cyanide (Fassett, 1963; Wilson, 1944).

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Aquatic Life Toxicology*

INTRODUCTION

Most of the toxicity data concerning the effects of acrylonitrile on freshwater aquatic life has been determined using static test conditions without measured concentrations. The 48-hour EC_{50} value for Daphnia magna and the 96-hour LC_{50} values for three fish species range from 7,550 to 33,500 µg/l, indicating that the range of sensitivity among these species is not great. However, it is not known whether other freshwater fish and invertebrate species are more or less sensitive to acrylonitrile exposure. Chronic lethal effects on one fish species were observed after 30 days with an LC_{50} value of 2,600 µg/l.

The only datum for saltwater organisms is a 24-hour LC_{50} for pinfish.

EFFECTS

Acute Toxicity

The only datum for freshwater invertebrate species is the 48-hour EC_{50} of 7,550 µg/l for Daphnia magna (Table 1).

Three freshwater fish species representing three families have been tested with acrylonitrile. In soft water static tests using unmeasured concentrations, the 96-hour LC_{50} values were 11,800 µg/l for the bluegill, 18,100 µg/l for the fathead minnow, and 33,500 µg/l for the guppy (Table 1). In addition, Henderson, et al. (1961) measured the sensitivity of the fathead minnow to acrylonitrile under different test conditions and water quality. The 96-hour LC_{50} value at a hardness of 380 mg/l as $CaCO_3$ and pH 8.2 was 14,300 µg/l while that at a hardness of 20 mg/l as $CaCO_3$ and pH 7.4 was 18,100 µg/l (Table 1). Changes in water quality within the range studied apparently did not affect the toxicity of acrylonitrile. Also, flow-through and static test conditions were compared using unmeasured concentrations, and the LC_{50} value for the fathead minnow was lower for the flow-through test (10,100 µg/l) than for the static test (18,100 µg/l).

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

Chronic Toxicity

Daphnia magna has been exposed for its life cycle and the results indicate no adverse effects at concentrations as high as 3,600 µg/l (Table 2). This concentration is only about one-half of the 48-hour EC_{50} (7,550 µg/l) for the same species under comparable conditions (U.S. EPA, 1978). This small difference between acute and chronic effects for *Daphnia magna* is unlike that relationship between acute and chronic effects for the fathead minnow. Henderson, et al. (1961), using flow-through methods and unmeasured concentrations, observed a 96-hour LC_{50} of 10,100 µg/l (Table 1) and when that test was continued the 30-day LC_{50} was 2,600 µg/l (Table 4).

Plant Effects

No freshwater or saltwater toxicity data are available for any plant species.

Residues

The bluegill was exposed for 28 days to ^{14}C-acrylonitrile with thin layer chromatography being used to verify exposure and tissue concentrations (U.S. EPA, 1978). The bioconcentration factor for whole body was 48 (Table 3) with a half-life in the tissues of between four and seven days.

Miscellaneous

As stated earlier, the 30-day LC_{50} for fathead minnows under flow-through conditions was 2,600 µg/l (Table 4), a result that is about one-fourth of the comparable 96-hour LC_{50} of 10,100 µg/l. Intermediate LC_{50}

values were 6,900 µg/l after 10 days and 4,200 µg/l after 20 days. These data suggest that mortality would continue to occur even after 30 days, further depressing the LC_{50} value. Henderson, et al. (1961) also exposed adult bluegill to 5,000 µg/l for 1 to 4 weeks and prepared the fish for a taste study panel (Table 4). No flavor impairment was detected at that concentration, which was almost one-half of the 96-hour LC_{50} value for the bluegill as determined by the same investigators. It is therefore unlikely that acrylonitrile will impair the flavor of freshwater fishes.

Summary

The data base for acrylonitrile is deficient in several important aspects. Acute toxicity data are lacking for planktonic or benthic crustaceans, benthic insects, detritivores, and salmonid fishes. Of the data available, only one of the 96-hour LC_{50} values for the fathead minnow was generated in a flow-through test, the rest being static tests; all acute tests used unmeasured concentrations. The range of EC_{50} and LC_{50} values is from 7,550 to 33,500 µg/l. The chronic data are limited to one inconclusive test with Daphnia magna and a 30-day LC_{50} value for the fathead minnow of 2,600 µg/l.

Despite these limitations, there is enough information available to indicate that acrylonitrile merits some consideration of its possible toxicological effects on freshwater aquatic life. In particular, these data suggest that acrylonitrile has a definite chronic or cumulative effect and that adverse effects can be expected to occur at concentrations below 2,600 µg/l in fish exposed to this compound for more than 30 days.

The only datum on saltwater species is a 24-hour LC_{50} value of 24,500 µg/l for the pinfish.

CRITERIA

The available data for acrylonitrile indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 7,550 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No definitive data are available concerning the chronic toxicity of acrylonitrile to sensitive freshwater aquatic life but mortality occurs at concentrations as low as 2,600 µg/l with a fish species exposed for 30 days.

Only one saltwater species has been tested with acrylonitrile and no statement can be made concerning acute or chronic toxicity.

Table 1. Acute values for acrylonitrile

Species	Method*	LC50/EC50 (µg/l)	Species Mean Acute Value (µg/l)	Reference
		FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	S, U	7,550	7,550	U.S. EPA, 1978
Fathead minnow, *Pimephales promelas*	S, U	14,300	-	Henderson, et al. 1961
Fathead minnow, *Pimephales promelas*	S, U	18,100	-	Henderson, et al. 1961
Fathead minnow, *Pimephales promelas*	FT, U	10,100	13,800	Henderson, et al. 1961
Guppy, *Poecilia reticulata*	S, U	33,500	33,500	Henderson, et al. 1961
Bluegill, *Lepomis macrochirus*	S, U	11,800	-	Henderson, et al. 1961
Bluegill, *Lepomis macrochirus*	S, U	10,100	10,900	U.S. EPA, 1978

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* S = static, FT = flow-through, U = unmeasured

No Final Acute Values are calculable since the minimum data base requirements are not met.

Table 2. Chronic values for acrylonitrile (U.S. EPA, 1978)

Species	Method*	Limits (µg/l)	Species Mean Chronic Value (µg/l)
	FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	LC	>3,600	-

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* LC = life cycle or partial life cycle

No acute-chronic ratio is calculable.

Table 3. Residues for acrylonitrile (U.S. EPA, 1978)

Species	Tissue	Bioconcentration Factor	Duration (days)
	FRESHWATER SPECIES		
Bluegill, *Lepomis macrochirus*	whole body	48	28

Table 4. Other data for acrylonitrile

Species	Duration	Effect	Result (µg/l)	Reference
		FRESHWATER SPECIES		
Fathead minnow, *Pimephales promelas*	30 days	LC50	2,600	Henderson, et al. 1961
Bluegill, *Lepomis macrochirus*	1-4 wks	No detectable flavor impairment of tissues	5,000	Henderson, et al. 1961
Bluegill (fingerling), *Lepomis macrochirus*	96 hrs	100% survival	10,000	Buzzel, et al. 1968
		SALTWATER SPECIES		
Pinfish, *Lagodon rhomboides*	24 hrs	LC50	24,500	Daugherty & Garrett, 1951

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Mammalian Toxicology and Human Health Effects

INTRODUCTION

Acrylonitrile is an explosive, flammable liquid having a normal boiling point of 77°C and a vapor pressure of 80 torr (20°C). The toxic effects of acrylonitrile are similar to cyanide poisoning although not identical. The chemical structure of acrylonitrile, CH_2=CHCN, resembles that of vinyl chloride, a material known to cause human cancer. Synonyms for acrylonitrile include cyanoethylene, 2-propenenitrile, VCN, and vinyl cyanide. Polymerization grade acrylonitrile contains a number of impurities and additives, namely, dimethylformamide, hydrogen peroxide, hydroxyanisole, methyl acrylate, phenyl ether-biphenyl mixture, sodium metabisulfite, sulfur dioxide, sulfuric acid, and titanium dioxide (O'Berg, 1977b).

At the present time, 1.6 billion pounds of acrylonitrile per year are manufactured in the United States by the reaction of propylene with ammonia and oxygen in the presence of a catalyst. (A number of other processes are used outside the United States.) Current domestic producers of acrylonitrile are American Cyanamid Company (New Orleans, Louisiana), E. I. du Pont de Nemours Company, Inc. (Beaumont, Texas and Memphis, Tennessee), Monsanto Company (Chocolate Bayou, Texas), and The Standard Oil Company (Lima, Ohio).

The major use of acrylonitrile is in the manufacture of copolymers for the production of acrylic and modacrylic fibers by copolymerization with methyl acrylate, methyl methacrylate, vinyl acetate, vinyl chloride, or vinylidene chloride. Acrylic fibers, marketed under tradenames including Acrilan®, Creslan®, Orlon®, and Zefran®, are used in the manufacture of apparel, carpeting, blankets, draperies, and upholstery. Some applications of modacrylic fibers are synthetic furs and hair wigs; tradenames for modacrylic fibers include Acrylan®, Elura®, SEF®, and Verel®. Acrylic and/or modacrylic fibers are manufactured from acrylonitrile by American Cyanamid Company (Milton, Florida), Dow Badishe Company (Williamsburg, Virginia), E. I. du Pont de Nemours and Company, Inc. (Camden, South Carolina and Waynesboro, Virginia), Eastman Kodak Company (Kingsport, Tennessee), and Monsanto Company (Decatur, Alabama) [National Institute for Occupational Safety and Health (NIOSH), 1977].

Other major uses of acrylonitrile include the manufacture of acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins (used to produce a variety of plastic products), nitrile elastomers and latexes, and other chemicals (e.g., adiponitrile, acrylamide). Acrylonitrile has been used as a fumigant; however, all U.S. registrations for this use were voluntarily withdrawn as of August 8, 1978 (43 FR 35099). The U.S. Food and Drug Administration (FDA) has recently banned the use of an acrylonitrile resin for soft drink bottles (Anonymous, 1976, 1977b, 1978), but its use is still allowed in other food packaging. NIOSH estimates that 125,000 persons are potentially exposed to acrylonitrile in the workplace (NIOSH, 1977).

At the present time, the body of evidence produced in both toxicity studies on laboratory animals and occupational epidemiologic studies on man suggests that acrylonitrile may be a human carcinogen. Thus, NIOSH has recently stated that "acrylonitrile must be handled in the workplace as a suspect human carcinogen" (NIOSH, 1978a). This judgment of NIOSH was based primarily on (1) a preliminary epidemiologic study of E. I. du Pont de Nemours and Company, Inc. of acrylonitrile polymerization workers from one particular textile fiber plant (Camden, South Carolina); in this study, it was ascertained that a substantial excess risk (twice that expected) of lung and colon cancers occurred between 1969 and 1975 in a cohort exposed between 1950 and 1955 (O'Berg, 1979); (2) interim results from ongoing 2-year studies on laboratory rats performed by the Dow Chemical Company, and reported by the Manufacturing Chemists Association (April, 1977) in which, by either drinking water (Quast, et al. 1980) or inhalation routes (Maltoni, et al. 1977) of acrylonitrile exposure, laboratory rats developed CNS tumors and Zymbal's gland carcinomas, not evident in control animals.

Aside from suggestive evidence of carcinogenicity in man and animals, other genotoxic characteristics of acrylonitrile (embryotoxicity, mutagenicity and teratogenicity) in laboratory animals have been reported (Venitt, et al. 1977; Milvy and Wolff, 1977; Murray, et al. 1976). Although there is some controversy over the chronic effects of acrylonitrile (Shaffer, 1977), the acute toxicity of acrylonitrile is well known and the compound appears to exert part of its toxic effect through the release of inorganic cyanide (Fassett, 1963; Wilson, 1944).

In this compilation of the human health effects and hazard evaluation of acrylonitrile, several reviews were consulted (Grahl, 1970; Fassett, 1963; NIOSH, 1978a). Much of the literature relating to occupational exposure and epidemiology is either Russian or East European in origin and, for the most part, only abstracts of these works were consulted.

Most of the work available regarding contamination of water supplies with acrylonitrile is in the foreign literature and deals primarily with either the use of polyacrylonitrile for filtration of industrial wastes or the biological treatment of waste effluents from acrylonitrile plants (Verkhovykh, et al. 1975; Skakihara, et al. 1976; Pradt and Meidl, 1976). Research regarding the monitoring of acrylonitrile in drinking water was not available for consideration. This is not unexpected because of the fact that only recently have the possible genotoxic effects of acrylonitrile been discovered.

Acrylonitrile is the most extensively produced aliphatic nitrile and ranks 45th on the list of high volume chemicals produced in the United States (Anonymous, 1978a). The 1976 production of acrylonitrile was 1.6 billion pounds (Anonymous, 1978b) which is approximately 7 times the 1960 production volume.

Approximately 125,000 individuals in the United States are exposed to acrylonitrile monomer during its manufacture and polymerization or during its molding to acrylonitrile-based polymers including Dralong T, Barex 210, Lopac, butadiene-acrylonitrile, and polyacrylonitrile (NIOSH, 1977). Disposal of acrylic polymers, including polyacrylonitrile, by burning results in the release of acrylonitrile monomer (Rumberg, 1971). Residual amounts of acrylonitrile monomer are released from fabrics such as underwear made of polyacrylonitrile fiber (Rapoport, et al. 1974), and from furniture and other items made of polyacrylonitrile plastics (Vol'skii, 1973). The public may also be exposed to acrylonitrile by ingestion of food products which have leached residual acrylonitrile monomer from polyacrylonitrile packaging materials, such as commercial plastic wraps for foods (Anonymous, 1977a).

Cigarette smoke has been shown by gas chromatographic analysis to contain aliphatic nitriles including acrylonitrile, propionitrile, and methacrylonitrile (Izard and Testa, 1968). The presence of aliphatic nitriles in cigarette smoke may explain why Mallette (1943) found higher values of thiocyanate (a known metabolic product of acrylonitrile) in the blood and urine of acrylonitrile works who were smokers compared to nonsmokers.

In summary, besides occupational exposure of those involved in the manufacture and processing of aliphatic nitriles, the public is exposed to acrylonitrile from the burning of acrylonitrile-based polymers, by release of residual monomer from acrylic fibers and plastics, by leaching of monomer from food packaging, and from cigarette smoke.

Some environmental monitoring for acrylonitrile has been reported by the Midwest Research Institute (MRI, 1978). Limited analyses of air, water, and soils at several sources and ambient locations throughout the United States resulted in the occasional detection of acrylonitrile. The values obtained are summarized in Table 1.

TABLE 1

Acrylonitrile Concentrations in Air, Soil, and Water from Various Locations in the U.S.[+]

Location (source)	Maximum Acrylonitrile Concentrations*		
	Air ($\mu g/m^3$)	Water** ($\mu g/l$)	Soil** ($\mu g/kg$)
Fortier, Louisiana (American Cyanamid)	13.6	0.1	0.5***
Linden, New Jersey (American Cyanamid)	15.9	0.8	50
Texas City, Texas (Monsanto)	8.9	0.4	none detected
Decatur, Alabama (Monsanto)	4.2	3,600	none detected
Camden, S. Carolina (du Pont)	1.1	20	none detected
Waynesboro, Virginia (du Pont)	7.0	none detected	none detected
Washington, West Virginia (Borg-Warner)	325	1.5	none detected

+ Source: Midwest Research Institute, 1978.

* Analysis were performed at various time intervals. Values given are maximum values. Some samples at the same location may be lower or non-detectable.

** Source of water or soil samples not indicated.

***Only one sample was found where acrylonitrile was at the detection limit of 0.5 mg/kg. All others were below detection.

EXPOSURE

Ingestion from Water

While no data on monitoring of water supplies for the presence of acrylonitrile were found in the literature, potential problems may exist. Because toxic manifestations in animals have been elicited by this route of administration, this source of exposure is potentially an important one.

There are limited data on the fate of acrylonitrile in the aqueous environment. It is known that acrylonitrile is water soluble (Table 2) and is hydrated readily at 100°C by 84.5 percent sulfuric acid to produce acrylamide sulfate (Kirk and Othmer, 1967). Whether this reaction occurs in the natural environment is unknown.

Acrylonitrile is known to undergo photodegradation to saturated derivatives. When left standing, especially in the presence of light, a yellow color may develop, possibly due to polymerization (Kirk and Othmer, 1967). Acrylonitrile is also subject to biodegradation (Kuchinskii, et al. 1977; Panova, et al. 1977; Anon, 1977; Schnee, et al. 1977; Kato and Yamamura, 1976; Mikami, et al. 1974). Measurement of biochemical oxygen demand has shown 25 to 70 percent degradation within 10 days (Hann and Jensen, 1970). Zabezhinskaya, et al. (1962) studied the persistence of acrylonitrile in the water column, noting that at an initial concentration of 10 mg/l, only 46 percent remained after 24 hours, 19 percent after 48 hours, and 5 percent after 96 hours. This would tend to minimize the ingestion of acrylonitrile in water. A study by Midwest Research Institute (1977) investigated the stability of 10 ppm

TABLE 2

Solubility of Acrylonitrile in Water as a Function of Temperature*

Temperature, °C	Solubility of Acrylonitrile in Water (grams/deciliter)
0	7.2
20	7.35
40	7.9
60	9.1

*Source: Kirk and Othmer, 1967.

acrylonitrile in distilled water and Mississippi River water. Little decomposition occurred after 23 days in distilled water. In river water, however, total decomposition occurred by day 6. Adjusting to a pH of 4 had a stabilizing effect in that 67 percent of acrylonitrile was present at 23 days. Adjusting to a pH of 10 delayed decomposition up to six days but total decomposition occurred by day 23.

Possible sources of acrylonitrile in the aqueous environment (either surface water, ground water, or drinking water) are: (a) dumping of chemical wastes; (b) leaching of wastes from industrial landfills or holding lagoons; (c) leaching of monomers from polymeric acrylonitrile; (d) precipitation from atmospheric rain; and (e) loss during transfer and transport (Hardy, et al. 1972). The first four sources listed are worthy of additional comment, and are discussed here.

Dumping of chemical wastes: Acrylonitrile monomer waste products are dumped by industrial companies directly into surface waters or sewage. Acrylonitrile has been used as a fumigant for stored foodstuffs either alone or in a mixture with carbon tetrachloride, (Fishbein, 1976), methylbromide (Dumas and Bond, 1977), and other chemicals (Heuser and Scudamore, 1968). Though no longer in use, stored quantities of these fumigants may be being dumped by the former manufacturers or the users.

The question of biotransformations of acrylonitrile in waste water, its effect on bacteria and particularly on biological sewage treatment processes such as the activated sludge treatment process are poorly understood. However, Chekhovskaya, et al. (1966) have observed the effects of acrylonitrile and related compounds on saprophytic microorganisms and bacterial processes of ammonification and nitrification. It was found that acrylonitrile at 150 mg/l (ppm) was utilized by saprophytic microorganisms and that acrylonitrile at 50 mg/l inhibited nitrification. This suggests that acrylonitrile, entering an activated sludge process in concentrations of 50 ppm or greater, may inhibit certain bacterial processes such as nitrification. Cherry, et al. (1956) reported that microbial activity could substantially reduce initial acrylonitrile concentrations of 10, 25, and 50 ppm. They noted also that while the two lower concentrations supported a mixed population of microorganisms, the 50 ppm concentrations favored the growth of fungi. This observation supports the findings of Chekhovskaya, et al. (1966) on inhibition of nitrification at 50 ppm and above. Other workers have shown similar reductions of acrylonitrile content in wastewater by microorganisms (Mikami, et al. 1974; Kato and Yamamura, 1976).

Leaching of wastes from industrial landfills or holding lagoons: Industrial chemical or pesticide wastes, placed in holding tanks or lagoons, may spill over into surface waters as a result of excessive rainfall. These same wastes may also be buried in industrial landfills. If the buried containers are damaged, rainfall may leach out the acrylonitrile, and providing that the soil is permeable, permit its movement into proximal ground water.

Leaching of monomers from polymeric acrylonitrile: It is well known that residual amounts of monomers are commonly retained in polymers; for example, vinyl chloride is leached out of PVC pipes and into drinking water (Dressman and McFarren, 1978). Russian investigators have reported that acrylonitrile and other monomers in finished polymers were detected in the range of 30 to 3,000 ppm (Klescheva, et al. 1970). Therefore, the acrylonitrile monomer can also be leached from waste polymers buried in landfills in the manner described above. Acrylonitrile is also leached by water from polyacrylonitrile plastic bottles [Natural Resources Defense Council (NRDC), 1976].

Precipitation of acrylonitrile from atmospheric rain: Acrylonitrile has a very high vapor pressure (112 torr at 25°C) (Kirk and Othmer, 1967). Therefore, it will volatilize substantially from various sources even at room temperature (see Inhalation section). Being present in the atmophere either as vapor per se or adsorbed to particulates, it is susceptible to precipitation from the atmosphere in rain or snow and eventually could be present in either surface or ground waters.

Release of acrylonitrile from transfer and transport accidents: Acrylonitrile may be spilled during the process of transfer and/or transportation, resulting in air and/or water contamination.

Ingestion from Food

The likelihood of acrylonitrile residues existing on food is high (Casarett and Doull, 1975; Fishbein, 1976; Dumas and Bond, 1977; Heuser and Scudamore, 1968). Dumas and Bond (1977) noted that acrylonitrile was desorbed very slowly from foods depending on the type of commodity and aeration conditions. Polyacrylonitrile containers (margarine containers, wrapping material, etc.) retain residual amounts of the monomer which may then be leached into the food and subsequently ingested by the consumer (NRDC, 1976).

Although FDA has banned the use of polyacrylonitrile plastic in soft drink bottles (Anonymous, 1976, 1977b, 1978), attempts to lift this ban by the producing companies are in progress. The FDA has restricted the monomer residue to about 80 ppm in the finished products and a restriction to 11 ppm was pending as of 1976 (NRDC, 1976). The currently produced soft drink container includes about 20 ppm acrylonitrile of which as much as 0.3 ppm acrylonitrile and 0.2 ppm HCN are reported to leach into hot water (NRDC, 1976).

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

A measured steady-state bioconcentration factor of 48 was obtained for acrylonitrile using bluegills (U.S. EPA, 1978). Similar bluegills contained an average of 4.8 percent lipids (Johnson, 1980). An adjustment factor of 3.0/4.8 = 0.625 can be used to adjust the measured BCF from the 4.8 percent lipids of the bluegill to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average BCF for acrylonitrile and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 48 x 0.625 = 30.

Inhalation

The current estimate in the U.S. for the number of individuals involved in the manufacture and polymerization of acrylonitrile is 125,000 (NIOSH, 1978b). Therefore, a considerable population is at high risk from occupational exposures, particularly through inhalation. Analyses of atmospheric air from an acrylic fiber plant in which a large fraction of the coworkers complained of symptoms of illness revealed concentrations of acrylonitrile of 3 to 20 mg/m^3 (Orusev and Popovski, 1973).

Workers involved in acrylonitrile synthesis or its polymerization are not the only occupational groups subject to acrylonitrile exposure; workers in plastic (polyacrylonitrile) molding factories are similarly at risk (Scupakas, 1968). Scupakas (1968) studied the working conditions in an old factory producing thermosetting plastics by molding and noted various toxic manifestations in employees including dermatitis, disorders of CNS, chronic upper respiratory tract irritation, and other symptomatology when the acrylonitrile concentration in the in-plant environment was 1.4 mg/m^3. However, various other compounds were present in the in-plant atmosphere including phenol, formaldehyde, ammonia, HCl, butyl phthalate, and carbon monoxide. Timofievskaya (1968) and Duvall and Rubey (1973) reported that various types of acrylonitrile polymers underwent decomposition to various nitriles, NO_x, unsaturated hydrocarbons, etc. either under molding conditions (40 to 400°C) or heating (40 to 80°C) and/or burning (200 to 600°C). The nature of the products formed were highly dependent on combustion conditions and contained significant amounts of highly toxic compounds. Some of the polymers studied included Dramalon T; polyacrylonitrile fiber; Barex 210 (3:1 acrylonitrile-methylacrylate copolymer); Lopac (9:1 methacrylonitrile-styrene copolymer); and 1,3 butadiene-nitrile rubber. It is clear that burning of acrylic polymers, including polyacrylonitrile, represents a great potential occupational and/or environmental hazard due to the release of high concentrations of acrylonitrile, other substituted vinyl compounds, HCN, NO_x, and other undetermined compounds (Table 3). In addition, it is likely that various significant interactions between the compounds occur (Hilado, et al. 1976; LeMoan and Chaigneau, 1977).

Though data are unavailable on monitoring the ambient atmosphere for the presence of acrylonitrile, the stack gases from synthesis and polymerization plants for acrylonitrile may well be discharging significant amounts into the atmosphere. As noted above,

TABLE 3

Pyrolysis of Lopac as a Function of Temperature Using Porapak N Column*

Pyrolysis Temperature(°C)	Pyrolysis Products
116	No compound observed
188	NH_3 (trace)
230	NH_3
260	NH_3
260	NH_3
290	NH_3
330	NH_3; HCN (trace); acrylonitrile
500	Air; CO; CO_2; C_2H_2; NH_3, HCN; acetonitrile, acrylonitrile, propionitrile; pyrrole
570	Air; CO; CO_2; C_2H_4; C_2H_2; NH_3; HCN; acetonitrile; acrylonitrile; pyrrole
740	Air; CO; CO_2; C_2H_4; C_2H_2; NH_3; HCN; acetonitrile; acrylonitrile; pyrrole

*Source: Monsanto, 1973.

another potentially significant ambient source of acrylonitrile and related compounds in air is the outside burning of acrylonitrile polymers. While it is known that acrylonitrile reacts photochemically in the vapor phase (Kirk and Othmer, 1967), no detailed data were available to the authors on the actual reactivity ($t_{\frac{1}{2}}$) of acrylonitrile in the atmosphere in ppm or ppb concentrations.

Vol'skii, et al. (1973) have noted that the amount of plastic and synthetic rubber furniture on boats must be limited to $<$ 10.8 kg of LKF-2 plastic/m^3 air to avoid an accumulation of monomers such as acrylonitrile vaporizing under the influence of the unusual combination of living conditions (humidity, heat, and light). The authors recommend adequate ventilation. Undoubtedly, the same findings apply to homes. In a recent report, Rapaport, et al. (1974) have indicated that traces of acrylonitrile were detected in the air surrounding underwear made from polyacrylonitrile fibers. Acrylonitrile, and a variety of other nitriles, have been found by gas chromatography to be components of cigarette smoke; the amounts were not quantified (Izard and Testa, 1968).

Inhalation has been reported to be the major route of exposure in lethal cases of acrylonitrile poisoning (Radimer, et al. 1974). When man breathes air containing 20 μg acrylonitrile/l (20,000 μg/m^3) the average retention of acrylonitrile vapors was found to be 46 percent (Rogaczewska and Piotrowsky, 1968). A later study by Young, et al. (1977) found with rats that retention was greater than 90 percent (see Pharmacokinetics section).

Dermal

Acrylonitrile has exhibited toxic effects on experimental animals by skin absorption (Hashimoto and Kanai, 1965; Egorov, et al. 1976). Anton'ev and Rogailin (1970) have reported that skin contact is one of the most important routes for acrylonitrile absorption in plant workers and that the absorption of acrylonitrile applied to the forearm skin averaged 0.6 mg/cm^2-hr. Egorov, et al. (1976) have determined the threshold doses for dermal absorption of acrylonitrile and other compounds in terms of a one-time application to the skin as well as a 4-month long chronic application. The value for acrylonitrile was estimated to be 0.11 mg/kg body weight. The maximum permissible contamination level for the skin of the hands of workers was determined to be 0.7 mg of acrylonitrile. It is not clear from the abstract whether the experiment was done on laboratory animals and extrapolated to man or performed directly on man. Dermatologic conditions including contact allergic dermatitis, occupational eczema, and toxodermia in acrylonitrile workers have been discussed by Dovzhanskii (1976a), Balda (1975), Malten (1973), and Anton'ev and Rogailin (1970) and show the importance of the dermal route in occupational exposure. That there is a hypersensitivity response to acrylonitrile has been discussed by Dovzhanskii (1976a), Balda (1975), and Khromov (1974).

Because of the paucity of data available on acrylonitrile, it is difficult to assess quantitatively the contribution of each route of exposure to the total dose in man; it is likely that the greatest contribution comes via inhalation, particularly in an occupational setting. The next most likely route is dermal and the least likely is ingestion. Figure 1 is a schematic representation of the various modes of exposure of man to acrylonitrile.

PHARMACOKINETICS

Absorption and Distribution

Attempts were not made to separate these categories due to the limited data available at the time of document preparation. Subsequently, a study on the pharmacokinetics of 1-^{14}C labeled acrylonitrile became available from the Manufacturing Chemists Association. Details of this study are included at the end of this chapter.

Blood concentrations of acrylonitrile and cyanide as a function of time after exposure have been studied in relation to toxicity (Hashimoto and Kanai, 1965). In the rabbit at a sublethal dose (30 mg/kg, LD_{50} = 75 mg/kg) a typical blood concentration versus time curve was observed. Acrylonitrile rapidly disappeared with 1 ppm of acrylonitrile remaining four hours after exposure. Thiosulfate accelerated the urinary excretion of thiocyanate (SCN^-) as a metabolite and somewhat reduced the toxicity of acrylonitrile; however, the blood concentration versus time curve was not changed (Hashimoto and Kanai, 1965). L-cysteine administered prior to acrylonitrile resulted in 80 percent reduction of acrylonitrile peak blood levels and 30 percent reduction of its toxicity. Unchanged acrylonitrile was detected in the urine of the rabbit 72 hours after exposure and in expired air one hour after dosing. In guinea pig urine, acrylonitrile was detected 24 hours after administration by gavage to 15 mg/kg. Urinary and expiratory excretion of unchanged acrylonitrile accounted respectively for only 3 and 10

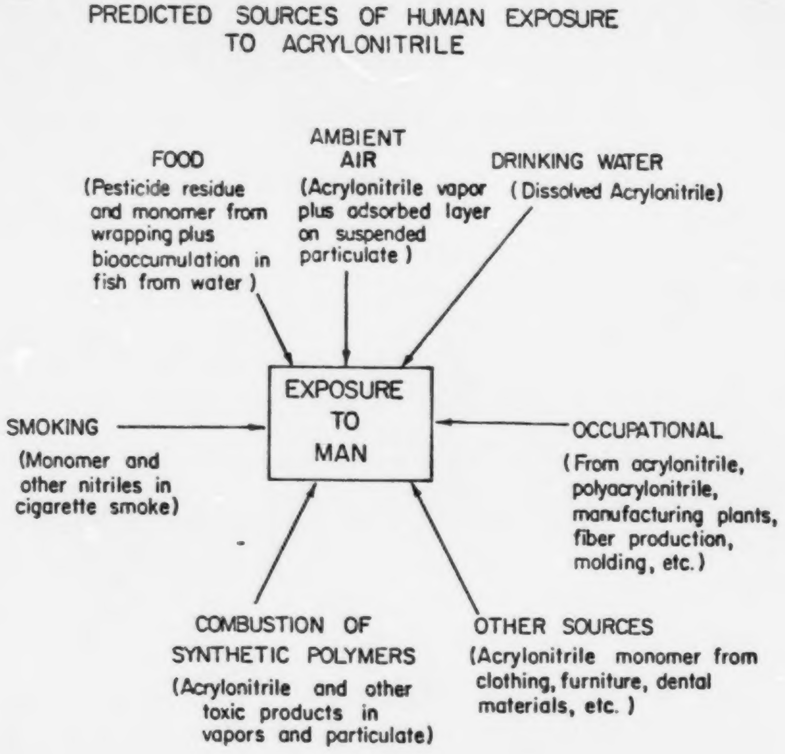
PREDICTED SOURCES OF HUMAN EXPOSURE TO ACRYLONITRILE
FOOD
(Pesticide residue and monomer from wrapping plus bioaccumulation in fish from water)
AMBIENT AIR
(Acrylonitrile vapor plus adsorbed layer on suspended particulate)
DRINKING WATER
(Dissolved Acrylonitrile)
EXPOSURE TO MAN
SMOKING
(Monomer and other nitriles in cigarette smoke)
OCCUPATIONAL
(From acrylonitrile, polyacrylonitrile, manufacturing plants, fiber production, molding, etc.)
COMBUSTION OF SYNTHETIC POLYMERS
(Acrylonitrile and other toxic products in vapors and particulate)
OTHER SOURCES
(Acrylonitrile monomer from clothing, furniture, dental materials, etc.)

FIGURE 1

Predicted Sources of Human Exposure

percent of the dose (15 mg/kg) while urinary thiocyanate accounted for 14 percent of the dose (Hashimoto and Kanai, 1965). The remainder was probably metabolized via direct enzymatic or nonenzymatic conjugation with nucleophilic compounds such as, cysteine, glutathione, and free or conjugated basic amino acids. Alternatively, the remainder may undergo enzymatic oxidation or reduction. A detailed metabolic study is required to elucidate the toxicokinetics of acrylonitrile.

Fat tissue accumulation of acrylonitrile may also occur. While the high solubility of acrylonitrile in water (7.35 percent at 20°C, Kirk and Othmer, 1967) would permit the excretion of the unchanged compound in the urine, the urinary detection 72 hours after exposure in the rabbit strongly suggests either fat storage or reversible protein binding. Czajkowska (1971) has studied the excretion of metabolites after a single intraperitoneal (i.p.) dose (60 to 70 mg/kg) of acrylonitrile in rats. The main urinary metabolite in rats was SCN^-; its excretion within 72 hours amounted to 8.5 percent of acrylonitrile intake. The SCN^- excretion half-life was 13 hours. No cyanide was detected in rat urine within 24 hours following the single dose, while only traces of acrylonitrile were observed.

Metabolism

Earlier reports (Giacosa, 1883; Meurice, 1900) indicated that most aliphatic nitriles are metabolized to cyanide which is then detoxified to thiocyanate. Levels of cyanide and thiocyanate were elevated in the blood and present in the urine of acrylonitrile-treated animals. Brieger, et al. (1952) observed elevated levels of cyanide, thiocyanate (SCN^-), and cyanomethemoglobin in the blood of animals treated with acrylonitrile. The author concluded that acrylonitrile exerts its toxicity by the metabolic release of cyanide ion, and that the relative ability of various species to convert CN^- to SCN^- determined their susceptibility to the toxic action of acrylonitrile (Brieger, et al. 1952). A later study by Boyland and Chasseaud (1967) indicates, however, that the toxicity of acrylonitrile is due in part to the molecule itself. It was found that the urinary excretion of thiocyanate after acrylonitrile administration ranged from 4 to 25 percent of the administered dose (Brieger, et al. 1952; Czajkowska, 1971; Gut, et al. 1975; Efremov, 1976; Paulet and Desnos, 1961; Benes and Cerna, 1959; Dudley and Neal, 1942; Hashimoto and Kanai, 1965). Brieger, et al. (1952) noted that in dogs (a species particularly susceptible to acrylonitrile), the relative concentration of cyanomethemoglobin increased with length of exposure, with most of the available methemoglobin converted to cyanomethemoglobin by the end of the lethal exposure period.

Using Wistar rats, albino mice, and Chinese hamsters, Gut, et al. (1975) found that the extent of conversion of acrylonitrile to cyanide was dependent on the route of administration, decreasing in the following order: oral ($>$20%) $>$ i.p. = s.c. (2 to 4%) $>$ i.v. (1%). Thus, the more slowly acrylonitrile enters the system, the more extensively it is converted to cyanide. This suggests that conversion of acrylonitrile to cyanide involves metabolic processes competing with blood protein binding and nonenzymatic cyanoethylation. Pretreatment of rats with phenobarbital, SKF 525A, cysteine, or dimercaprol (BAL) did not significantly influence elimination of SCN^- in the urine after acrylonitrile administration; however, simultaneous administration of thiosulfate and acrylonitrile significantly increased the metabolized portion (thiocyanate) of acrylonitrile given to rats by twofold and mice by threefold. Pretreatment with Aroclor® 1254 was found to greatly enhance the toxicity of acrylonitrile, and to cause a threefold increase in the cyanide level in the blood of treated rats; Gut, et al. (1975) found acrylonitrile to be strongly bound in blood. Acrylonitrile was metabolized to SCN^- more effectively by mice than by rats following oral, i.p., and intravenous (i.v.) administration. Possible differences in the mechanism of acrylonitrile toxicity in rats and mice are indicated by the greater metabolism of acrylonitrile to SCN^- and the larger decrease in its acute toxicity by thiosulfate in mice compared with rats. Gut, et al. (1975) concluded that cyanide may play a more important role in the toxicity of acrylonitrile in mice than it does in rats.

In their study, Gut, et al. (1975) offered no explanation for the role of cysteine on the acrylonitrile SCN^- balance, nor do they explain cysteine's protective mechanism against acrylonitrile toxicity. If cysteine is protecting the animal by reaction with acrylonitrile via formation of cyanoethylcysteine, thiocyanate levels should decrease, and if it enhances cyanide metabolism, thiocyanate levels should increase. However, pretreatment with cysteine had no effect on thiocyante levels.

In vitro, it was implicated that acrylonitrile was conjugated with glutathione (GSH) via a GSH transferase enzyme. The conjugate of this reaction was not detected; rather conjugation was measured indirectly by disappearance of the GSH substrate (Boyland and Chasseaud, 1967). Although uptake of acrylonitrile gives rise to a slight increase in cyanomethemoglobin, combined therapy with nitrite and thiosulfate affords partial protection against its toxic action. These facts suggest that acrylonitrile toxicity is due in part to the acrylonitrile molecule itself or other unknown metabolite(s) rather than just the cyanide functional group. Only traces of unchanged acrylonitrile were detected in the urine of acrylonitrile-treated rats (Czajkowska, 1971). This suggests that the major portion of the compound is altered in the body to other metabolites or conjugates such as indicated in the following scheme proposed.

Proposed pathways for acrylonitrile biotransformation are presented in Figure 2 (A. Ahmed, personal communication). Cyanoethylated products (top pathway) of cell macromolecules and of circulating nucleophiles can be recovered in tissue fractions and in biologic fluids. If the proposed pathway is correct cyanoethylated glutathione conjugates should be recoverable in bile and urine. One, in fact, has been found - cyanoethylated mercapturic acid (A. Ahmed, personal communication). Oxidation by the mixed function oxidases or another enzyme system could lead to an epoxide which could be enzymically hydrated, could rearrange, or be acted upon by glutathathione transferase. In either case, soluble oxidized products would be produced and cyanide would be liberated. Products of the proposed oxidation pathways, including glyoxalic acid, oxalic

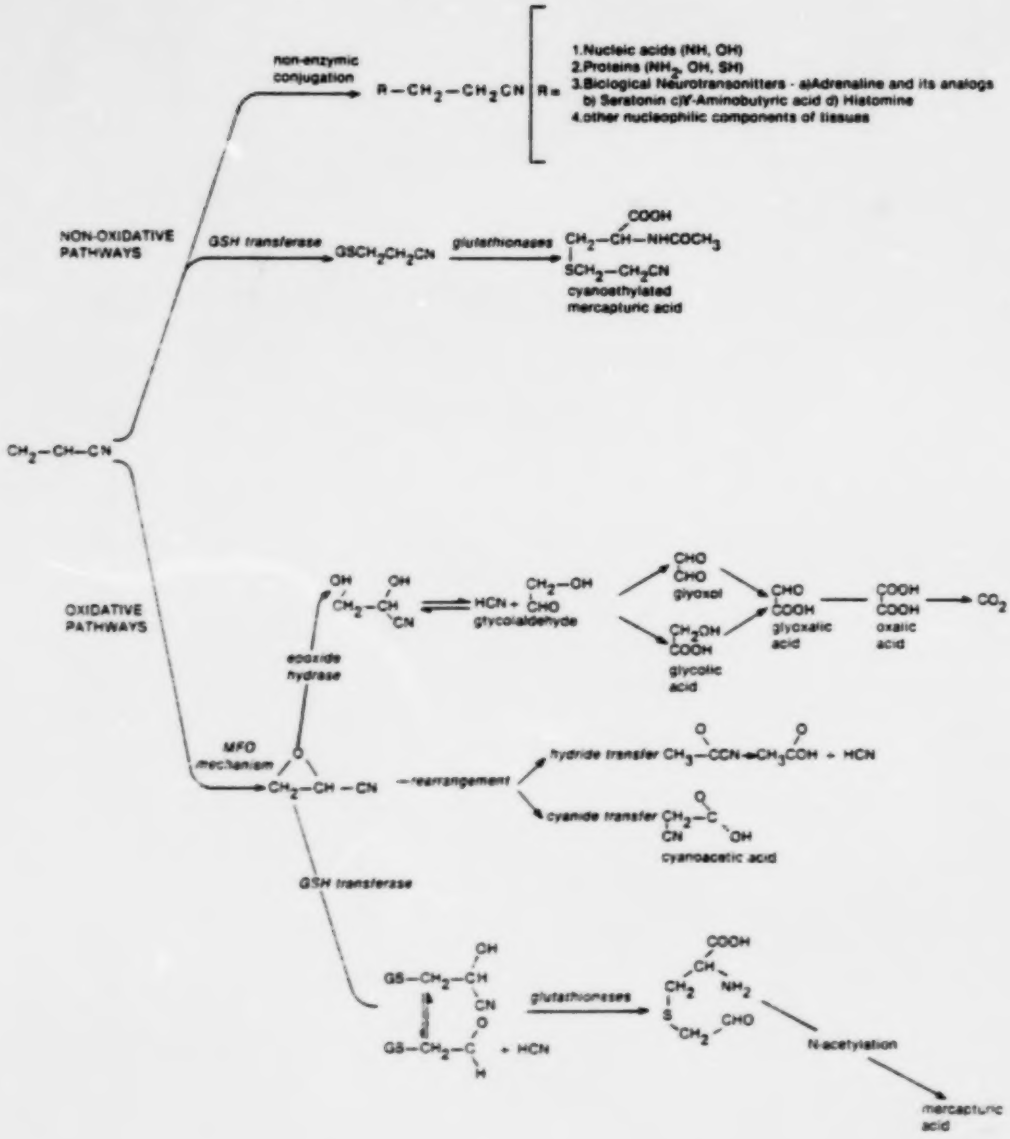
non-enzymic conjugation
$R-CH_2-CH_2CN$
R=
1.Nucleic acids (NH, OH)
2.Proteins (NH_2, OH, SH)
3.Biclogical Neurotransonitters - a)Adrenaline and its analogs b) Seratonin c)γ-Aminobutyric acid d) Histomine
4.other nucleophilic components of tissues
NON-OXIDATIVE PATHWAYS
GSH transferase
$GSCH_2CH_2CN$
glutathionases
COOH
$CH_2-CH-NHCOCH_3$
SCH_2-CH_2CN
cyanoethylated mercapturic acid
$CH_2-CH-CN$
OXIDATIVE PATHWAYS
OH
OH
CH_2-CH
CN
HCN +
CH_2-OH
CHO
glycolaldehyde
CHO
CHO
glyoxol
CH_2OH
COOH
glycolic acid
CHO
COOH
glyoxalic acid
COOH
COOH
oxalic acid
CO_2
epoxide hydrase
MFO mechanism
O
$CH_2-CH-CN$
rearrangement
hydride transfer
$CH_3-\overset{O}{C}CN \rightarrow CH_3\overset{O}{C}OH$ + HCN
cyanide transfer
CH_2-C
CN
O
OH
cyanoacetic acid
GSH transferase
OH
$GS-CH_2-CH$
CN
O
$GS-CH_2-C$
H
+ HCN
glutathionases
COOH
CH
CH_2
NH_2
S
CHO
CH_2
N-acetylation
mercapturic acid

FIGURE 2

Proposed Pathways for Acrylonitrile Biotransformation acid, acetic acid, cyanoacetic acid, and cyanide are soluble and should be detectable in blood or urine.

Most recently, Young, et al. (1977) published the results of a comprehensive radiotracer study in which 1-^{14}C labeled acrylonitrile was used in male Sprague-Dawley rats to determine dose and route dependency of the pharmacokinetics of this compound. The position of the radiotag allowed tracking of the three carbon chain metabolites as well as the one carbon cyano moeity. Three major routes of administration were used with the following dose variations:

Route	Doses	
Ingestion via single oral dose of aqueous solution.	0.1 mg/kg	10 mg/kg
Inhalation of 6 hours duration from a "nose only" chamber	5 ppm Calc. mean dose = 0.7 mg/kg	100 ppm 10.2 mg/kg
Intravenous injection	10 mg/kg	

The major conclusions of this study are highlighted in the following:

Absorption: When orally administered to rats, essentially all of the acrylonitrile is absorbed and metabolized. Only 5 percent of the dose is excreted with the feces in the form of metabolites.

Metabolism: Qualitatively, CO_2 and three unidentified metabolites, A, C, and E were identified in the rat. These metabolites (A, C, and E) were excreted primarily in the urine, while CO_2 was primarily exhaled with breath. Chemical identities of compounds A, C, and E were not elucidated, but contrary to prior suspicion none of these were acrylamide. Metabolite C predominated at low doses followed by compound A while molecule E was present in trace quantities. This ratio changed at high dose when A drastically increased. Recovery of total radioactivity in metabolites, A, C, E, and CO_2 exceeded 94 percent.

Distribution: The metabolites of acrylonitrile were rapidly distributed to all tissues. Plasma concentration of radioactivity remained at similar levels without regard to route or dose. Metabolites E and C were reabsorbed from the small intestine and metabolite E underwent enterohepatic circulation. The enterogastric and enterohepatic phenomena could account for the retention of the radioactivity in the body. Metabolite E was found in the erythrocytes, where its half-life was significantly longer than in other storage sites. This latter observation suggests that metabolite E forms adducts with red cell constituents. This in turn may imply that the red cell serves as an accumulator of chronic acrylonitrile insult in the body, and therefore may be used for biological monitoring of exposure. Independently of dose or route of administration metabolite E was selectively accumulated in the stomach (glandular and nonglandular portion of the stomach wall).

Even after the total body burden of ^{14}C declined and after the ^{14}C concentration of stomach contents diminished, the stomach uptake remained at a positive slope. This finding reinforces phenomena previously observed in rats, namely the emergence of gastric papillomas even though the route of exposure was other than oral.

In a similar fashion the skin accumulated acrylonitrile metabolites which rose to 2 to 3 times over plasma levels. Possible interfering effects of skin absorption from the exogeneous gas phase must be discounted because the investigators used a "nose only" type of inhalation chamber. While the mechanism of skin absorption is unknown, it is plausible that the abundance of the sulfhydryl groups in the skin protein matrix may be responsible for the effects seen.

Dose dependency of metabolism: Metabolite C was found to be the main liver metabolite, which after bile excretion was readily re-absorbed from the small intestine and excreted in the urine. Only a very small portion of the total dose-load appeared in the form of compound A. After administration of high doses however, compound A strikingly increased. The formation of metabolite E was time dependent and did not occur significantly in the first eight hours after administration. An in vitro study using rat liver homogenate (9,000xg) supernate indicated that the liver is not the chief site for the formation of compound E. In addition, the very early appearance of metabolite E in the red cells suggests extrahepatic sites (perhaps a red cell enzyme) for the formation of this molecule.

CO_2 could arise as a product of cyanate metabolism. Although thiocyanate was shown to be the main product of cyanide metabolism (Boxer and Richards, 1952) these authors have shown that cyanide can be metabolized to carbon dioxide via the cyanate ion. In fact, this study demonstrated a strong dose dependence of cyanide metabolism in dogs. It is plausible that the dose dependence of acrylonitrile pharmacokinetics may result in part from differences in the fate of the cyanide formed.

Excretion

The dose and route dependent variations in the metabolic fate of acrylonitrile are most likely due to shifts in metabolic pathways associated with hepatic and extrahepatic origin. Therefore the authors conclude: "extrapolation of the results of toxicological studies conducted by one route to expected toxicity at the same dosage by another route (a common practice) may not be valid for acrylonitrile because of its route dependent fate; likewise, extrapolation from toxicological data at one dose level to a different, untested, dose level cannot be done with confidence because of the dose dependent fate of acrylonitrile in the body".

This conclusion creates some uncertainty in the use of the linear nonthreshold model for calculating the acceptable risk concentration in water for man exposed to acrylonitrile (see Carcinogenicity section). However, the data presented by Young, et al. (1977) did not indicate that the metabolites whose fate was dose-dependent was necessarily the cancer inducing material. Therefore, until these data are experimentally developed the linear model can still be applied.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Dudley and Neal (1942) reported that a 4-hour exposure by inhalation to 635 ppm acrylonitrile was fatal to rats, while a 4-hour exposure to a lower level, 100 ppm, was fatal to dogs. Subsequent animal experiments have shown that acrylonitrile is acutely toxic by all routes of administration including inhalation, oral, subcutaneous and cutaneous exposure (NIOSH, 1978b).

Table 4 lists the toxic effect levels for different species (NIOSH, 1977). Acrylonitrile toxicity varies between species (Wilson and McCormick, 1949). Mice are very sensitive to acrylonitrile and suffer a severe decrease in body weight with a slight change in blood picture (Hashimoto, 1962). Benes and Cerna (1959) observed that rats have higher resistance to acrylonitrile exposure; they developed delayed symptoms and high levels of thiocyanate in urine and blood. Dudley, et al. (1942) reported that inhalation exposure of rats to 56 ppm x 4 hours, 5 days a week, for 8 weeks resulted in irritation of the respiratory mucous membrane with hyperemia, lung edema, alveolar thickening, and hemosiderosis of the spleen. Central nervous system disorders were also observed.

A 90-day toxicity study, conducted by Dow Chemical Company, incorporating 200 and 300 ppm of acrylonitrile in the drinking water of rats resulted in the animals' death before the end of the study (NRDC, 1976). Knobloch, et al. (1972) observed a perceptible change in peripheral blood pattern, functional disorders in the respiratory and cardiovascular systems and the execretory nephron system as well as signs of neuronal lesion in the CNS of rats and rabbits breathing acrylonitrile (50 mg/m^3 air) for six months. In addition, they reported irritation of the mucosa when acrylonitrile concentration in the air was increased to 250 mg/m^3. Graczyk and Zwierzchowski (1973) reported that i.v. administration of 13 to 110 mg acrylonitrile decreased the pressor effects of epinephrine, norepinephrine, and acetylcholine. When injected s.c. at 0.5 mg/rat/day for 10 days, acrylonitrile decreased the rate of O_2 uptake and increased that of glycolysis in brain (Solov'ev, et al.

TABLE 4

Toxic Levels of Acrylonitrile for Different Species*

Species	Route	Effect	Dose
Rat	Oral	LD_{50}	82 mg/kg
	Inhalation	LCLo	500 ppm/4 hr
	S.C.	LD_{50}	96 mg/kg
Mouse	Oral	LD_{50}	27 mg/kg
	Inhalation	LCLo	784 ppm/1 hr
	I.P.	LDLo	10 mg/kg
Dog	Inhalation	LCLo	110 mg/kg/4 hr
Cat	Inhalation	LCLo	600 ppm/4 hr
Rabbit	Oral	LD_{50}	93 mg/kg
	Inhalation	LCLo	258 ppm/4 hr
	Skin	LD_{50}	250 mg/kg
Guinea Pig	Oral	LD_{50}	50 mg/kg
	Inhalation	LC_{50}	576 ppm/4 hr

*Source: NIOSH, 1978b.

1972). Acrylonitrile did not effect the levels of ATP or creatinine phosphate. Solov'ev, et al. (1972) also reported an increase in the activity of phosphofructokinase and a decrease in the glycogen level in cerebral tissue.

Knobloch and Szendzikowski (1971) reported that the LD_{50}s of acrylonitrile in rats were 80 and 100 mg/kg when given s.c. and i.p., respectively, and 34 mg/kg when given s.c. to mice. When inhaled with air over three weeks, the LC_{50}s of acrylonitrile were 0.3, 0.47, and 0.99 mg/l in mice, rats and guinea pigs, respectively (Knobloch and Szendzikowski, 1971). They also reported that acrylonitrile caused congestion and damage to the CNS, lungs, liver, and kidneys. Intraperitoneal injections of 50 mg acrylonitrile/kg daily for three weeks to adult rats resulted in body weight loss, leukocytosis, functional disturbances in liver and kidneys, slight damage to the neural cells of the brain stem and cortex, and parenchymal degeneration of the liver and kidneys (Knoblock and Szendzikowski, 1971). Krysiak and Knobloch (1971) reported that acrylonitrile (20 mg/kg/day for six weeks or 40 mg/kg/day for four weeks) caused disturbances in the central nervous system of rats as evidenced by misperformance in the labyrinth test. In that test acrylonitrile caused marked impairment of food-conditioned reflexes and learning ability. Babanov, et al. (1972) reported that inhalation of acrylonitrile vapor (0.495 mg/m^3, 5 hours/day, 6 days/week) for six months resulted in CNS disorders and an abnormal blood picture (increased erythrocyte count and decreased leukocyte count) in rats. It also resulted in increased total protein catalase and peroxidase content, decreased ascorbic acid content of blood serum and increased number of free sulfhydryl groups in the liver and blood serum. Acrylonitrile given orally in a dose of 80 mg/kg increased the content of several amino acids in the brain (Movsumzade, 1970). In the same study Movsumzade reported that, in the liver, various pools of basic amino acids levels were decreased to traces. He related these observations to the damage of synthetic function of the liver and to damage of the blood-brain barrier. Takagi, et al. (1968) studied the effect of administration of vitamins B_1 or B_2 plus cysteine to rats exposed to acrylonitrile vapor over a long period. They observed that urinary excretion of thiocyanate decreased with this treatment. They reported that exposure to acrylonitrile caused enlargement of liver, kidney, heart, and spleen and a decline of alcohol dehydrogenase activity in the liver; alleviation of these symptoms occurred upon administration of vitamin B_1 or B_2 plus cysteine. A single s.c. administration to rats of acrylonitrile at two times the LD_{50} dose decreased the liver and kidney glutathione level greatly and increased levels of lactic acid (Dinu and Klein, 1976). These authors also reported that catalase activity was slightly increased but only in the liver. They concluded that the decrease of reduced glutathione levels rendered the glutathione peroxidase ineffective, and the increase of lactic acid concentration concomitantly inhibited a compensatory increase in catalase activity. The resulting increase in the peroxide level damaged the tissue. Dinu (1975) reported that similar doses of acrylonitrile administered orally to rats increased the hepatic levels of malonaldehyde, glutathione peroxidase and catalase, which she concluded, indicate lipid peroxidation.

Tissue protein and nonprotein sulfhydryl (reduced glutathione) decreased in guinea pigs and rabbits following a single dose of acrylonitrile (Hashimoto and Kanai, 1965; Szabo, et al. 1977; Dinu, 1975). Prior treatment with thiol compounds such as cysteine, confers some protection against the toxic action of acrylonitrile (Paulet, et al. 1966; Hashimoto and Kanai, 1965). An increase in the number of free sulfhydryl groups was also observed in the liver and serum of rats chronically treated with acrylonitrile (Babanov, et al. 1972; Szabo, et al. 1977). *In vitro* inhibition of potassium-stimulated respiration of brain cortex was observed at a 10^{-3}M acrylonitrile concentration; little effect on liver respiration was observed (Hashimoto and Kanai, 1965). Tarkowski (1968) reported that cytochrome oxidase was inhibited in liver, kidney, and brain tissue taken from rats two hours after i.p. administrations of 100 mg/kg acrylonitrile. In Tarkowski's *in vitro* experiments with similar tissues, inhibitions of 18 to 30 percent, 45 to 55 percent, and 75 to 85 percent with 10^{-4}, 10^{-3}, and 10^{-2}M acrylonitrile, respectively, were obtained. Since acrylonitrile did not change the spectrum of cytochrome oxidase in the same manner as KCN, Tarkowski concluded that the toxic effect of acrylonitrile could not be attributed to generation of cyanide. Minami, et al. (1973) reached just the opposite conclusion. They reported what they thought to be a high degree of similarity between the response of rabbits poisoned by acrylonitrile and rabbits poisoned by cyanide; the blood pO_2, pCO_2, pH, hemoglobin, and hemotocrit values were correlated with the concentration of cyanide and thiocyanate.

Wilson and McCormick (1949) reported that acrylonitrile shows large variations in toxicity among species. In rabbits, extensive damage in the four phases of the brain nervous system was observed. Other symptoms were shivering, tearing, redness of the ears, and hyperemia (Benes and Cerna, 1959). Dudley, et al. (1942) reported that guinea pigs treated with acrylonitrile (1.25 mg/l) developed strong interstitial nephritis, bronchopneumonia, and inflammatory lung irritation. Dogs were the most sensitive experimental animals to acrylonitrile (Grahl, 1970). Thiocyanate levels in serum and urine of dogs treated with 100 ppm acrylonitrile were 10 times higher than those of rats receiving the same dose (Lawton, et al. 1943; Lindgren, et al. 1954). Liver and kidney damage was less pronounced in the dogs than in rats (Brieger, et al. 1952). In monkeys, anoxia, brain damage, and death by suffocation were observed upon administration of acrylonitrile (Grahl, 1970). Acrylonitrile intoxication in cats resulted in the early onset of liver injury (Dudley, et al. 1942). Pathologic examination of animals following acute acrylonitrile exposure revealed all animals had edema (Dudley and Neal, 1942; Szabo and Selye, 1971a); histologic changes in the brain, particularly the cortex, characteristic of anoxia (Brieger, et al. 1952); blood that was unusually dark red and liquid (Dudley and Neal, 1942; Brieger, et al. 1952); and liver and kidney damage (Knobloch, et al. 1972). Pathologic examination following repeated acrylonitrile administration revealed slight damage to the neural cells of the brain stem and cortex, and parenchymal cell degeneration of the liver (Knobloch and Szendzikowski, 1971). Repeated acrylonitrile administration was also associated with weight loss, leukocytosis, and functional disturbances of liver, kidney, and adrenal cortex (Knobloch and Szendzikowski, 1971; Szabo, et al. 1976). Szabo and Selye (1971a,b) reported that adrenal apoplexy and necrosis were produced in rats by administration of a single oral dose of acrylonitrile (100 to 200 mg/kg); 100 percent mortality was observed. The adrenals of the dead animals showed hemorrhages in the cortex and necrosis in the inner cortical zones. Acrylonitrile induced-adrenal apoplexy, and mortality in female rats were both prevented by pretreatment with phenobarbital and adrencorticotrophic (ACTH) hormones (Szabo and Selye, 1971b, 1972). Szabo and Selye (1972) also reported that the adrenal lesion was abolished by potent glucocorticoids, especially dexametamethason and betamethason. Estradiol prevented adrenal apoplexy in approximately half the animals treated with a single lethal dose of acrylonitrile (Szabo and Selye, 1972). The mechanism by which these drugs interfered with the acrylonitrile induced injury is not clear. Nevertheless, structure-activity relationships exist between ACN and other nitriles and other alkyl compounds which cause duodenal ulcers and/or adrenal necrosis (Szabo and Reynolds, 1975).

A two year toxicity and carcinogenicity study with acrylonitrile incorporated in drinking water of rats was conducted by Quast, et al. (1980).

In this study, male and female Sprague-Dawley rats maintained for two years on drinking water containing acrylonitrile at 35, 100, or 300 ppm showed a variety of toxic effects. Increasing concentrations of acrylonitrile in the drinking water resulted in decreased water consumption, decreased food consumption, and decreased weight gain, in a dose-related fashion in both male and female rats.

Periodic hematologic determinations indicated that there was no evidence of adverse hematologic effects caused by ingestion of drinking water containing acrylonitrile at the concentration used in this study.

Periodic urinalyses of male and female rats indicated a treatment-related effect in the urine specific gravity in the 100 and 300 ppm groups. The increase in urine specific gravity indicates that the kidneys were capable of concentrating the urine, and this was considered to be an adaptation in physiological function to compensate for the rats' limited daily water consumption.

Clinical chemistry determinations used to evaluate kidney and liver function revealed that neither organ system was adversely affected in rats ingesting water containing acrylonitrile.

Clinical evidence of altered nervous system function was noted in treated rats and usually correlated with the presence of a brain tumor upon microscopic examination of the tissues. Furthermore, clinical manifestations of irritability were more readily apparent in the rats ingesting water containing acrylonitrile. Whether this apparent irritability was a direct effect of acrylonitrile on the CNS or a result of stress related to the decreased water and food consumption could not be ascertained.

The necropsy findings and subsequent histopathologic examinations of tissues of male rats revealed a variety of pathologic alterations which occur with greater or lesser frequency in acrylonitrile-treated than in the respective control group of rats. Changes of a nontumorous nature in the kidneys of male rats revealed that advanced chronic renal disease, which normally occurs with increasing frequency in aged rats, was less frequently seen in the 100 and 300 ppm groups of rats, when compared to the control group.

Many other organ systems showed a concurrent decrease in the incidence of those pathologic changes which normally occur as a result of the advanced chronic renal disease. In general, in the 300 ppm group and less frequently in the 100 and 35 ppm groups, there was a decreased incidence of degenerative vascular changes in most organs, decreased uremic mineralization of the stomach, decreased uremic encephalopathy, decreased parathyroid gland hyperplasia, decreased lung changes associated with renal disease, decreased left atrial thrombosis of the heart, decreased severity of focal myocardial degeneration and fibrosis, and decreased aortic thickening and mineralization. The incidence of atrophy of the mediastinal fat was increased in the 300 ppm group, and was due to the decreased nutritional state of these rats. An increase in splenic extramedullary hematopoiesis was also observed in the 300 ppm group of rats.

Microscopic lesions which were considered related to acrylonitrile treatment were observed, with statistically significant increased frequency, in the nonglandular gastric mucosa and the endocardium of the heart. Lesions in the nonglandular gastric mucosa were characterized by hyperplasia and hyperkeratosis and were observed more frequently and in a dose-related fashion in the 100 and 300 ppm group of male rats. In the endocardium there was evidence of an increased incidence of endocardial disease in the 300 ppm group.

Few human studies, other than cancer epidemiology, were found for U.S. workers. Therefore, the majority of studies cited are from the foreign literature.

The human threshold of smell to acrylonitrile lies between 8 to 40 mg/m^3 (3.7 to 18.5 ppm), and a quick tolerance is always developed after repeated inhalation (Fairhall, 1957). A point of unbearability was reached at 800 to 1,000 mg/m^3 (370 to 460 ppm) sometime after 70 seconds of exposure (Grahl, 1970). The high threshold of smell and the high absorptive capacity of environmental objects (such as textiles, wood, food, and grain) to acrylonitrile acts to minimize the perception of acrylonitrile and so intensify the degree of exposure, and consequently the toxicity.

Goncharova, et al. (1977) reported that examinations of 689 persons engaged in the production of acrylonitrile in the USSR evidenced effects of acrylonitrile upon the heart. In their studies Shirshova, et al. (1975) indicated that workers with long service records in the acrylonitrile polymer industry showed decreases in hemoglobin level and a trend to leukopenia and relative lymphocytosis. Stamov, et al. (1976) studied the working environment and health state of workers involved in the production of polyacrylonitrile fibers (Burgas, Bulgaria) where dimethylformamide was also present. Their studies indicated that in exposed workers there is a tendency towards diseases of the peripheral nervous system, stomach, duodenum, and skin.

In an epidemiologic study of health impairment among acrylonitrile workers in Japan, Sakarai and Kusimoto (1972) studied 576 workers exposed over a 10-year period (from 1960 to 1970) to acrylonitrile in concentrations of 5 to 20 ppm. The cohort was studied with respect to: (a) age and length of exposure to acrylonitrile, (b) subjective complaints, as well as (c) objective symptoms. They found increased incidences of subjective complaints including headache, fatigue, nausea, and weakness; as well as clinical symptoms of anemia, jaundice, conjunctivitis, and abnormal values of specific gravity of whole blood, blood serum and cholinesterase values, urobilinogen, bilirubin, urinary protein, and sugar. These clinical values were found to vary directly with length of exposure to acrylonitrile and differences were significantly different from normals. Sakarai and Kusimoto (1972) concluded that acrylonitrile exposures at these levels caused mild liver injury and probably a cumulative general toxic effect.

The working conditions and health status of operators engaged in the production of acrylonitrile were studied by Ostrovskaya, et al. (1976), where the working area atmosphere was polluted by acrylonitrile as well as other chemicals. In those workers, changes in the heart and circulation, blood methemoglobin content, and increased excretion of glucuronic acid occurred during working hours.

Zotova (1975) in the USSR reported that the concentration of acrylonitrile in the air of the plant he studied exceeded by 5- to 10-fold the "maximal permissible concentration" (i.e., hygienic goal; 0.435 mg/m^3), and he recommended the enforcement of lower levels for the compound. He reported the blood of workers in contact with acrylonitrile, when compared with control values, had a lower content of erythrocytes, leukocytes, hemoglobin, and sulfhydryl groups.

Shustov and Mavrina (1975) reported that medical examination of 340 workers and clinical studies of the blood and other biological fluids of 50 workers in polyacrylonitrile production plant showed symptoms of poisoning in the majority of the workers. They found that workers complained of headaches, vertigo, fatigue, insomnia, and skin itching. The clinical studies showed that the majority of the workers had functional disorders of the central nervous system, cardiovascular, and hemopoietic systems. The degree of pathological change increased with years of service in the plant (Shustov and Mavrina, 1975).

Dovzhanskii (1976a,b), Khromov (1974), and Balda (1975) reported contact allergic dermatitis and changes in immunoglobulin levels upon direct contact with acrylonitrile and other acrylate components of synthetic fabrics. Mavrina and Il'ina (1974) reported that students of an industrial training school who came in contact with acrylates (mainly acrylonitrile) at atmospheric levels of 0.8 to 1.8 mg/m^3 showed disturbed immunological reactivity and sensitization. The positive allergic reactions in persons not having signs of allergic diseases indicated latent allergy (premorbid phase) developing at various times after contact with acrylonitrile. Because of the considerable sensitivity of young people, sensitization by these substances can develop within several days after the start of the training (Mavrina and Il'ina, 1974).

Recently Radimer, et al. (1974) reported four cases in which toxic epidermal necrosis developed 11 to 21 days after patients returned to houses fumigated with a 2:1 mixture of carbon tetrachloride and acrylonitrile; this mixture was once widely used as a pesticide in Florida homes (Radimer, et al. 1974). In these cases, four patients were hospitalized with blisters covering almost the entire skin surface and mucous membranes. Administration of antibiotics, corticosteroids, fluids, and electrolytes produced no improvement in the three adult female patients. These three patients died of septic shock and gastrointestinal hemorrhage 3 to 4 weeks after exposure (Radimer et al. 1974). They also reported that the 10-year-old son of one of these patients developed widespread pruritic eruptions, but survived with topical and parenteral corticosteroid application. The possibility that carbon tetrachloride, rather than acrylonitrile, was the responsible agent for the observed toxicity cannot be excluded absolutely (Radimer, et al. 1974). Hardy, et al. (1972) reported an impaired pulmonary function following a railroad accident in which a crew of four railroad engineers suffered an intense single exposure to unknown amounts of acrylonitrile. After the exposure, weakness was the chief symptom followed by dyspnea on exertion when the workers returned to normal activity. Pulmonary function testing done seven years after exposure indicated that lung damage was still present in all four workers and had probably originated at the time of the accident (Hardy, et al. 1972). Two additional cases of mortality following acute acrylonitrile exposure have been reported. Both involved children, one treated with acrylonitrile for scalp lice and the other sleeping in a room fumigated with acrylonitrile (Grunske, 1949).

Toxicological studies give no clear insight into the possible mechanisms of acute and subacute acrylonitrile toxicity. Although Tarkowski (1968) proposed some evidence favoring a cyanide-mediated effect, there is also evidence against it (Paulet, et al. 1966). Earlier reports indicated that cyanide liberation is responsible for acrylonitrile toxicity (Desgrez, 1911; Wagner-Jauregg, et al. 1948). Mediation of acrylonitrile toxicity by cyanide was considered because of the following observations noted upon acrylonitrile administration: (a) increased blood and urine thiocyanate concentration (Mallette, 1943; Wilson, et al. 1948; Lawton, et al. 1943); (b) appearance of free cyanide and cyanomethemoglobin in blood (Hashimoto and Kanai, 1965; Brieger, et al. 1952); (c) slight similarities to the toxicity symptoms and histopathologic results produced by administration of hydrocyanic acid and its salts; (d) successful use of some cyanide antidotes in treatment of some toxic symptoms resulting from acrylonitrile administration (Dudley, et al. 1942; Hashimoto and Kanai, 1965; Levina, 1951; Yoshikawa, 1968). Other hypotheses have attributed the toxicity of acrylonitrile to the intact molecule (Schwanecke, 1966; Paulet, et al. 1966; Ghiringhelli, 1954; Desgrez, 1911; Graham, 1965; Magos, 1962;

Benes and Cerna, 1959). Support for these hypotheses comes from the following observations: (a) no correlation between acrylonitrile toxicity in guinea pigs or rats with either blood levels of cyanide ions and cyanomethemoglobin or the amount of thiocyanate excreted in urine (Ghiringhelli, 1954, 1956; Magos, 1962); (b) no free cyanide ions detected in the blood of guinea pigs exposed to acrylonitrile (Dudley and Neal, 1942; Dudley, et al. 1942); (c) histopathologic aberrations after acrylonitrile exposure not explicable as cyanide action (Dudley, et al. 1942; Benes and Cerna, 1959); (d) controversial reports on the action of specific cyanide antidotes, e.g., hydroxycobalamine, sodium nitrites, and sodium thiosulfate in treatment of acrylonitrile poisoning (McOmie, 1943; Ghiringhelli, 1954; Magos, 1962; Hashimoto and Kanai, 1965).

Benes and Cerna (1959) postulated that in acrylonitrile sensitive animal species, quick decomposition of the entire acrylonitrile molecule to cyanide ion takes place and a typical cyanide toxicity is produced. However, Brieger, et al. (1952) reported that high SCN/CN ratios were observed in acrylonitrile sensitive animals.

Paulet, et al. (1966) reported that the toxic action of acrylonitrile in rabbits and guinea pigs is only partially due to cyanide liberation. It has been suggested that additional biotransformation may contribute partially to acrylonitrile's acute toxicity (Paulet, et al. 1966; Benes and Cerna, 1959). Desgrez (1911) in his earlier studies suggested a role for the conjugated double bond in acrylonitrile toxicity.

Szabo, et al. (1980) investigated the pathogenesis of experimental adrenal hemorrhagic necrosis produced by acrylonitrile in the rat. One dose of this chemical injected intravenously caused 100 percent incidence of adrenal hemorrhage and necrosis in 90 to 120 minutes. Electron microscopy, histochemistry, and light microscopy combined with colloidal carbon labeling suggested an early damage (30 minutes after administration of acrylonitrile) to the vascular endothelium in the adrenal cortex, prominent at 60 minutes, when lesion to the parenchymal cells was not visible. The use of extracellular diffusion tracer horseradish peroxidase further indicated that parenchymal cell injury was a late event. Damage to the vascular endothelium in the adrenal cortex was associated with retrograde embolization of medullary cells and cell fragments into the cortical capillaries. The ultrastructurally demonstrated platelet aggregation and fibrin precipitation at the sites of discontinuous vascular endothelium were accompanied by a decrease in circulating platelets and fibrinogen as well as prolongation of prothrombin, partial thromboplastin, and thrombin time. The concentration of dopamine, unlike that of noradrenaline, in the adrenals but not in the brain of rats injected with acrylonitrile showed a time-dependent elevation. Pretreatment with phenoxybenzamine (α-adrenergic antagonist) or labetalol (α- and β-adrenergic blocker) or metyrapone (11-β-hydroxylase inhibitor) and the depletion of catecholamines by reserpine or prior medullectomy prevented the chemically induced adrenal necrosis. These results indicate that the presence of a functional adrenal cortex is necessary for the development of cortical damage which is associated with early vascular lesions caused and/or modulated by vasoconstrictive amines from the medulla and/or (metabolites of) acrylonitrile.

A number of other hypotheses have been developed to describe the mechanism of acrylonitrile toxicity (Hashimoto and Kanai, 1965; Ghiringhelli, 1954; Magos, 1962). They suggest the blocking by cyanoethylation of important sulfhydryl group containing enzymes. This hypothesis was supported by the excellent antidotal action of cysteine and glutathione in guinea pigs and mice (Paulet, 1966; McLaughlin, et al. 1976). A general blocking effect upon cell metabolism together with irreversible inhibition of the respiratory enzymes have also been described as possible mechanisms of acrylonitrile toxicity (Ghiringhelli, 1954, 1956). Acrylonitrile is known to deplete hepatic glutathione (Szabo, 1977). Dinu (1975) suggested that a decrease in hepatic glutathione levels renders the glutathione peroxidase ineffective, and the resulting increase in the peroxide levels damages the hepatic cells.

Synergism and/or Antagonism

Standard antidotes against cyanide poisoning have been used in attempts to abate the acute toxicity of acrylonitrile. Dudley and Neal (1942) found that neither sodium thiosulfate nor methylene blue afforded any protection against acrylonitrile lethality, while injection of sodium nitrite had a protective and antidotal action against the severity of symptoms (particularly the respiratory distress) and the lethality if given immediately before or after acrylonitrile exposure. This protective and antidotal action was observed for dogs, rats, and rabbits but not for guinea pigs. Ghiringhelli (1954) found that guinea pigs were not protected against acrylonitrile toxicity by the anticyanide treatments tested: glucose, sodium thiosulfate, and nitrite. Using another antidote for cyanide poisoning, hydroxycobalamin, Graham (1965) found that prior treatment of mice or dogs reduced the immediate (two hours) lethality of acrylonitrile but increased the lethality at 24 hours. McLaughlin, et al. (1976) found that the combination of sodium nitrite with sodium thiosulfate was not effective against acrylonitrile lethality for mice, dogs, and rats and only moderately effective in rabbits, while sodium thiosulfate alone was very effective rats and less effective for rabbits. Cysteine hydro chloride was the most effective of all antidotes against acrylonitrile lethality in all species tested by McLaughlin, et al. (1976).

Other kinds of treatments have been reported to affect the acute toxicity of acrylonitrile. Jaeger, et al. (1974) reported that acrylonitrile's LC_{50} for fasted rats was approximately three times lower than that for fed rats (150 vs 425 ppm x 4 hours). Szabo and Selye (1972) reported phenobarbital pretreatment diminished the acute adrenal apoplexy caused by acrylonitrile, and Paulet, et al. (1966) reported the same treatment delayed its lethality. HCN and CO were found to enhance acrylonitrile toxicity in experimental animals (Yamamoto, 1976) as well as in workers engaged in the acrylonitrile production (Ostrovskaya, et al. 1976).

Teratogenicity

Murray, et al. (1976) reported that their studies on Sprague-Dawley rats demonstrated a potential for acrylonitrile to cause fetal malformation when it was given to pregnant rats by gavage at high dose levels (65 mg/kg/day or approaching the LD_{50}) on gestational days 6 to 15. Though sialodacryoadenovirus infection (murine mumps) occurred in both experimental and control animals, it is unlikely that this had an effect on the teratogenicity findings. At administration of 65 mg acrylonitrile/kg/day Murray, et al. (1976) found significant maternal toxicity and increased fetal malformations, including acaudea, short-tail, short trunk, missing vertebrae, and right-sided aortic arch (Tables 5 and 6). Other signs of embryo toxicity or fetotoxicity at this dose level were decreased fetal body weight and crown-rump length and increased incidences of minor skeletal variants. At the time of Cesarean section, observations were made which are included in Table 7. The apparent pregnancy rate, i.e., the proportion of bred rats with visible implantation sites at the time of Cesarean section was significantly lower among rats given 65 mg acrylonitrile/kg/day than among the control rats. Administration of acrylonitrile had no significant effect on the litter size, the fetal sex ratio or the incidence or distribution of resorptions. At 65 mg/kg/day, the fetal body and crown-rump length were significantly lower than control values. No statistically significant effect was observed at the doses 10 and 25 mg/kg/day.

In Table 5 the incidence of external or soft tissue alterations among litters of rats given various doses of acrylonitrile by gavage is indicated. At 65 mg/kg/day the frequency of acaudate

TABLE 5

Incidence of Fetal Alterations Observed During the External or Soft Tissue Examination Among Litters of Rats Receiving Acrylonitrile by Gavage*

		Dose Level of Acrylonitrile, mg/kg/day[a]			
		0	10	25	65
		No. Fetuses/No. Litters Examined			
External Examination		443/38	388/35	312/29	212/17
Soft Tissue Examination		154/38	135/35	111/29	71/17
External Examination		% Affected (no. affected)			
Acaudate	F[b]	0	0	0.6(2)	2(4)[c]
Acaudate or short tail	F	0.2(1)	0	0.6(2)	4(8)[c]
	L	3(1)	0	7(2)	35(6)
Short trunk	F	0	0	0	1(3)[c,d]
	L	0	0	0	18(3)
Imperforate anus	F	0	0	0	1(2)[d]
	L	0	0	0	12(2)
Soft Tissue Examination					
Right-sided aortic arch	F	0	0	1(1)	1(1)[d]
	L	0	0	3(1)	6(1)
Ovaries, anteriorly displaced	F	0	0	1(1)[d]	1(1)[d]
	L	0	0	3(1)	6(1)
Missing kidney, unilateral	F	1(1)	0	0	1(1)[d]
	L	3(1)	0	0	6(1)
Dilated renal pelvis, unilateral	F	0	0	2(2)	0
	L	0	0	7(2)	0
Dilated ureter, left	F	0	0	1(1)	1(1)[d]
	L	0	0	3(1)	6(1)

TABLE 5 (Continued)

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*Source: Murrary, et al. 1976.

[a] Acrylonitrile was given by gavage on days 6-15 of gestation.

[b] F = fetuses; L = litters.

[c] Significantly different from control by a modified Wilcoxon test, $p<0.05$.

[d] This alteration occurred only in fetuses with a short or missing tail at this dose level.

TABLE 6

Incidence of Skeletal Alterations Among Litters of Rats Receiving Acrylonitrile by Gavage*

		Dose Level of Acrylonitrile, mg/kg/day[a]			
		0	10	25	65
		No. Fetuses/No. Litters Examined			
Skeletal Examination		443/38	388/35	312/29	212/17
Skull Bone Examination		289/37	253/34	201/24	141/17
Skeletal Examination		% Affected (no. affected)			
Vertebrae - 12 thoracic and 5 lumbar (normal no. is 13 T and 6 L)	F[b]	2(7)	0	2(7)	0
	L	3(1)	0	7(2)	0
-missing vertebrae other than 1 thoracic and 1[c] lumbar[c]	F	0.2(1)[d]	0	0.6(2)[d]	4(8)[d,e,]
	L	3(1)	0	7(2)	35(6)
-missing centra of cervical vertebrae (other than C_1 and C_2)	F	5(23)	8(30)	10(31)	34(71)[e]
	L	29(11)	46(6)	46(13)	88(15)
Ribs -missing 13th pair only	F	2(7)	0	2(7)	0
	L	3(1)	0	7(2)	0
-missing more than 1 pair[g]	F	0	0	1(2)[d]	2(4)[d,e]
	L	0	0	7(2)	24(4)

TABLE 6 (Continued)

Sternebrae - delated ossification, 5th	F	2(9)	3(13)	4(13)	15(31)[e]
	L	16(6)	23(8)	34(10)	59(10)
-missing, 5th	F	0	0	1(2)	1(2)
	L	0	0	7(2)	12(2)
-split, 5th	F	1(4)	1(3)	1(3)	4(8)
	L	10(4)	9(3)	10(3)	30(5)
-split, 2nd	F	0	0	0	2(4)[e]
	L	0	0	0	24(4)
Skull Bone Examination					
-delayed ossification any skull bone	F	7(21)	6(15)	6(12)	4(5)
	L	30(11)	26(9)	29(7)	18(3)

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*Source: Murrary, et al. 1976.

[a] Acrylonitrile was given by gavage on days 6-15 of gestation.

[b] F - fetuses; L - litters.

[c] The actual number of thoracic, lumbar and sacral vertebrae of each of the affected fetuses were as follows (normal no. is 13 T, 6 L, 4 S): Control - 12T, 2L, OS; 25 mg/kg/day - 2T, OL, OS, 2T, 1L, 1S; 65 mg/kg/day -13T, 3L, OS; 3T, OL,)S; 13T, 6L, 2S; 7T, 3L, OS; 13T, 3L, OS; 2T, OL, OS; 3T, OL, OS; 13T, 5L, 4S.

[d] This alteration occurred only among fetuses with short or missing tail at this dose level.

[e] Significantly different from control by a modified Wilcoxon test, $p<0.05$.

[f] This alteration occurred only among fetuses with 12 thoracic and 5 lumbar vertebrae.

[g] The affected fetuses exhibited 0-7 pairs of ribs (normal no. is 13).

TABLE 7

Observations Made at the Time of Cesarean Section of Rats Receiving Acrylonitrile by Gavage*

	Dose Level of Acrylonitrile, mg/kg/day[a]			
	0	10	25	65
Number of bred females	43	39	33	29
Number of deaths/no. of females	0/43	0/39	0/33	1/29
Apparent pregnancy rate[b]	88% (38/43)	90% (35/39)	89% (29/33)	69% (20/29)[c,d]
Total pregnancy rate[e]	88% (38/43)	90% (35/39)	89% (29/33)	83% (24/29)
Proportion of pregnant animals detected only by sulfide staining[f]	(0/38)	(0/35)	(0/29)	17% (4/24)[d]
Number of litters	38	35	29	18
Implantation sites/dam[g, h]	12±3	12±3	11±4	12±3
Live fetuses/litter[g,h]	12±3	11±3	11±4	12±3
Resorptions/litter[g,h]	0.7±0.9	0.6±0.8	0.4±0.6	0.6±0.7
% Implantations resorbed[h]	6% (26/469)	5% (21/409)	3% (11/323)	4% (10/222)
Litters with resorptions[h]	47% (18/38)	40% (14/35)	34% (10/29)	44% (8/18)
Litters totally resorbed[h]	0	0	0	1
Resorptions/litters with resorptions[h]	1.4(26/18)	1.5(21/14)	1.1(11/10)	1.2(10/8)
Sex ratio, M:F	49:51	49:51	48:52	53:47
Fetal body weight, g[i]	5.68±0.28	5.78±0.25	5.80±0.33	5.26±0.32[j]
Fetal crown-rump length, mm[i]	44.4±1.0	44.5±1.3	45.0±1.2	43.6±1.2[j]

TABLE 7 (Continued)

LEGEND

[a] Acrylonitrile was given by gavage on days 6-15 of gestation.

[b] No. of females with visible implantation sites at the time of cesarean section or necropsy/total no. of bred females.

[c] A female which delivered her litter on day 20 of gestation was included in the calculation of the pregnancy rates. The litter was not examined for fetal alterations.

[d] Significantly different from control by Fisher's exact probability test, $p \leq 0.05$.

[e] No. of females with implantation sites as observed either visually at the time of cesarean section or after staining the uterus with sodium sulfide stain/total no. of bred females.

[f] No. of females with implantation sites detected only after staining the uterus with sodium sulfide stain/total no. of females with implantation sites.

[g] Mean ± S.D.

[h] Data from the four females in which implantation sites were detected only after sodium sulfide staining of the uterus were not included in these calculations.

[i] Mean of litter means ± S.D.

[j] Significantly different from control mean by Dunnett's test, p 0.05.

*Source: Murrary, et al. 1976.

fetuses among litters was significantly higher than the control incidence. Also at this dose level, a statistically significant increase in the combined incidence of acaudate and short-tailed fetuses was observed. There were no statistically significant differences in the frequency of either of these tail anomalies alone or combined among litters of rats given the lower doses levels (10 or 25 mg/kg/day).

The soft tissue examination indicated right-side aortic arch in single fetuses at both 25 and 65 mg/kg/day (see Table 5).

The incidence of skeletal alterations among litters of rats given acrylonitrile by gavage is summarized in Table 6. The incidence of skeletal alterations among litters of rats receiving 10 or 25 mg acrylonitrile/kg/day were not significantly different from control litters. At 65 mg/kg/day, a significant increase was seen in the frequency of fetuses missing vertebra(e) other than a single thoracic and single lumbar vertebra. Also at this dose, each acaudate or short-tailed fetus (and only these fetuses) had this defect, ranging in severity from missing a single lumbar vertebra to missing 12 thoracic, all lumbar, and all sacral vertebra. In addition, the incidence of fetuses missing more than one pair of ribs was significantly higher than control litters (see Table 6).

An additional study by Murray, et al. (1978) concluded that when Sprague-Dawley rats were exposed to 0, 40, or 80 ppm of acrylonitrile by inhalation, teratogenic effects in the offspring of pregnant rats were suggested at 80 ppm but not 40 ppm. Significant maternal toxicity was found at both 80 and 40 ppm.

A three-generation reproduction study of rats receiving acrylonitrile in drinking water conducted by Litton Bionetics, Inc. was conducted to evaluate the effect of acrylonitrile on the reproductive capacity of rats (Beliles, et al. 1980).

The reproductive indices are summarized in Table 8. It should be noted that the F3b viability index at 100 ppm, while statistically significant, was higher than the control. Further analysis by the Mantel-Haenszel method combining Chi-square analysis showed a significant decrease in both the viability and lactation indices for the high dose group (500 ppm). Upon review, the single instance in which the viability index of the 100 ppm group was significantly lower than the control, (Flb) was not judged to constitute a meaningful effect.

The histopathologic evaluation of the adult females revealed a high frequency of unusual tumor types (Table 9). In conclusion, the results of this three-generation study suggest that:

1. Acrylonitrile at 500 ppm reduced body weight gain and food intake of the first generation parent rats (FO);
2. The pup survival at the 500 ppm treatment level for both matings of the first generation was reduced. Further analysis indicated the viability and lactation indices were reduced at the 500 ppm level throughout the entire study. Fostering the pups onto untreated mothers lessened mortality of the pups, suggesting a maternal effect. There was no remarkable change on the reproductive capacity at 100 ppm;

TABLE 8

Summary of Reproductive Indices*

Mating	Treatment	Male Fertility		Female Fertility		Gestation		Viability		Lactation	
		Ratio	Percent	Ratio	Percent	Ratio	Percent	Ratio	Percent	Ratio	Percent
F1a	0	10/10	100	18/20	90	18/18	100	185/186	94	138/50	92
	100	8/10	80	16/20	90	16/16	100	197/201	98	139/150	93
	500	10/10	100	16/20	80	16/16	100	166/177**	94	95/143**	66
F1b	0	10/10	100	16/20	80	16/16	100	186/186	100	137/150	91
	100	10/10	100	17/20	85	17/17	100	182/202**	90	132/139	95
	500	13/15	87	22/28	79	22/22	100	99/109**	91	87/99	88
F2a	0	5/10	50	10/20	50	10/10	100	107/109	98	91/91	100
	100	7/10	70	11/20	55	11/11	100	116/124	94	95/104**	91
	500	8/10	80	14/20	70	14/14	100	133/140	95	107/114**	94
F2b	0	6/10	60	10/20	50	10/10	100	101/101	100	82/82	100
	100	5/10	50	8/20	40	8/8	100	93/97	96	70/73	96
	500	8/10	80	14/20	70	14/14	100	138/138	100	123/123	100
F3a	0	6/10	60	14/20	70	14/14	100	161/161	100	128/131	98
	100	9/10	90	13/20	65	13/13	100	157/158	99	124/124	100
	500	10/10	100	15/20	75	15/15	100	157/166**	95	134/135	99
F3b	0	9/10	90	14/20	70	14/14	100	170/176	97	106/108	98
	100	10/10	100	15/20	75	13/13	100	198/198**	100	117/119	98
	500	10/10	100	17/20	85	17/17	100	170/180	94	115/125	92

*Source: Beliles, et al. 1980.
**$p<0.05$ [4].

TABLE 9

Astrocytoma and Zymbal's Gland Incidence

Generation	Astrocytoma/Rat Dose (ppm) 0	 100	 500
FO	0/19	1/20	2/25
Flb	0/20	1/19	4/17*
F2b	0/20	1/19	1/20
Total	0/59	3/59	7/62*

Generation	Zymbal's Gland Tumor/Rat Dose (ppm) 0	 100	 500
FO	0/19	0/20	1/25
Flb	0/20	2/19	4/17*
F2b	0/20	0/20	3/20
Total	0/59	2/59	8/62*

*Source: Beliles, et al. 1980.
**$p < 0.05$.

3. In all three generations, the body weights of the 500 ppm treatment level were reduced on day 21 for both matings (Table 10);
4. Upon gross and microscopic evaluation, no adverse findings were observed in the tissues of third generation weanlings (F3b);
5. No effect on the sciatic nerve was evident among the adult female rats held for 20 weeks after weaning of the second litter;
6. A dose-related tumorigenic effect of acrylonitrile in the drinking water in female rats held 20 weeks after the weaning of the second litter was suggested by the gross observations; and
7. Histopathologic evaluation of these dams showed an increase in astrocytomas and Zymbal's gland tumors (Table 10).

Mutagenicity

The mutagenicity of acrylonitrile to various organisms has been described by several investigators. Benes and Sram (1969) noted only weak effects in *Drosophila melanogaster* and concluded that acrylonitrile toxicity towards the species limited the testing. Milvy and Wolff, (1977) reported that in various strains of *Salmonella typhimurium* activated by mouse liver homogenate, acrylonitrile is mutagenic in the TA 1535 tester strain that is sensitive to base substitution, as well as strains TA 1538 and TA 1978, which are sensitive to frameshift mutagens. No dose-response data were obtained, however, and high reversion rates were seen in the

TABLE 10

Effect of Acrylonitrile Treatment on Pup Weights

Generation	Dose Level (ppm)	Mean Pup Weight (g)	
		Day 4	Day 21
F1a	0	11	42
	100	10	40
	500	9*	28*
F1b	0	10	38
	100	9	35
	500	10	34*
F2a	0	11	39
	100	10	39
	500	9*	30*
F2b	0	11	51
	100	10	46
	500	9	30*
F3a	0	10	43
	100	9	43
	500	8*	30*
F3b	0	10	49
	100	10	46
	500	8*	32*

*Source: Beliles, et al. 1980.
**$p < 0.05$.

controls. Milvy and Wolff reported that the presence of the activating system and NADPH cofactor is a prerequisite for acrylonitrile-induced mutagenesis (Milvy and Wolff, 1977).

In a comprehensive study Venitt, et al. (1977) concluded that acrylonitrile is a mutagen for *Escherichia coli* strains WP2, WP2 µvrA, and WP2 µrvApolA. Acrylonitrile caused a slight dose-related increase in the number of revertant colonies compared with untreated bacteria in 3 of the 4 strains. WP2 lexA was not detectably reverted by acrylonitrile. Of the three strains showing a statistically significant mutagenic response, WP2 was slightly more sensitive to the mutagenic effect of acrylonitrile, showing a fourfold increase over the spontaneous levels compared with a threefold increase for WP2 µvrA and a twofold increase for WP2 µvrApolA. Doses above 150 µmol per plate caused a decline in mutagenic response, concomitant with increasing toxicity as shown by a dose-related reduction in the density of the bacterial lawn. An important observation reported by Venitt, et al. (1977) was that the addition of a metabolizing system *in vitro* (S-9 mixture prepared from the liver of Aroclor® 1254-induced CB hooded male rats) had no detectable effect on the mutagenic action of acrylonitrile. Therefore, they concluded that acrylonitrile is a directly acting mutagen in these strains of *E. coli*.

The differential response of the tested strains to the mutagenic action of acrylonitile suggests that acrylonitrile causes nonexcisable DNA damage (Venitt, et al. 1977; Green, 1976). Acrylonitrile has been shown to cyanoethylate ring nitrogen atoms of certain minor tRNA nucleosides and ribothymidine and thymidine

(Ofengand, 1967, 1971). Accordingly, Venitt, et al. (1977) suggested that acrylonitrile might react with thymine residues in DNA.

Carcinogenicity

A 2-year toxicity and carcinogencity study with acrylonitrile incorporated in drinking water of rats was conducted by Quast, et al. (1980).

In this study, male and female Sprague-Dawley rats maintained for two years on drinking water containing acrylonitrile at 35, 100, or 300 ppm showed a variety of toxic effects. Increasing concentrations of acrylonitrile in the drinking water resulted in decreased water consumption, decreased food consumption, and decreased weight gain, in a dose-related fashion in both male and female rats.

Monthly examination and palpation of the rats was performed to evaluate the presence of detectable masses indicative of tumor formation. Tumors found in these examinations suggested that after 12 months an increased number of rats in the high dose group had ear canal gland (Zymbal's gland) tumors or subcutaneous tumors in the mammary region. These observations were initially noted in rats ingesting the highest dose level of acrylonitrile and were subsequently observed in the two lower dose groups also. The ear canal gland tumors grew progressively larger, ulcerated, bled from their surface, and caused deviation of the lower jaw.

The total number of primary tumors and number of rats with a primary tumor found upon microscopic examination of tissues from male and female rats maintained for two years on drinking water containing acrylonitrile are summarized in Table 11.

TABLE 11

Summary of Primary Tumor Incidence*

ppm AN in Water	% of Rats with a Tumor		Number of Tumors per Rat Bearing a Tumor	
	Male	Female	Male	Female
0	67/80 = 83.8	78/80 = 97.5	152/67 = 2.27	250/78 = 3.20
35	37/47 = 78.7	47/48 = 97.9	84/37 = 2.27	191/47 = 4.06
100	47/48 = 97.9	48/48 = 100	152/47 = 3.23	217/48 = 4.52
300	46/48 = 97.9	48/48 = 100	178/46 = 3.87	217/48 = 4.52

*Source: Quast, et al. 1980.

The data reveal that ingestion of water containing acrylonitrile statistically significantly increased the incidence of total tumors in male rats in the 100 and 300 ppm groups. The number of tumors per rat bearing a tumor appears to be increased in all dose groups in the females and at the middle and high dose groups in the males.

Gross observations of tumorous changes which were statistically significant in treated male rats are presented in Table 12. The ear canal gland (Zymbal's gland), tongue, nonglandular portion of the stomach, and brain were recognized as tissues with significantly increased number of tumors in the 300 ppm group. In the 100 ppm group the tongue and nonglandular portion of the stomach also showed a significantly increased tumor incidence. In the 300 ppm group the incidence of adrenal gland tumors was significantly decreased.

Histopathologic observations of tumors in the central nervous system (CNS), pituitary, thyroid, and adrenal glands which were observed to be statistically significantly different in treated male rats are summarized in Table 13. A significantly increased incidence of a CNS tumor, characterized as an astrocytoma, was observed in rats in all dose groups. In addition, a significantly increased incidence of a focal or multifocal glial cell proliferation suggestive of an early tumor of the same cell type was observed in the 35 and 300 ppm groups.

The proliferative process in the CNS was observed most frequently in the cerebral cortex, followed by brain stem in the region of the cerebellum, and less frequently in the cerebellum and

TABLE 12

Gross Observations of Tumorous Changes Which Were Statistically Significant in Male Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

Observation	Dose Level (ppm)		
	35	100	300
Integument and Subcutaneous Tissue			
Subcutaneous tumor - ear canal (Zymbal's gland)	-	-	Inc.
Tumor or tumor-like proliferation of the tongue	-	Inc.	Inc.
Gastrointestinal Tract			
Gastric tumor - nonglandular region, focal papilloma ≤ 2 in tumor	-	Inc.	Inc.
Gastric tumor - nonglandular region, focal papilloma >2 in tumor	-	Inc.	Inc.
Gastric tumor - total number of rats with a primary tumor involving any part of the stomach	-	Inc.	Inc.
Adrenal Gland			
Enlarged unilateral or bilateral, with or without associated color changes, suggestive of tumor	-	-	Dec.
Nervous System			
Brain - focal changes in consistency or color suggestive of primary tumor	-	-	Inc.

*Source: Quast, et al. 1980.

Results are listed on the basis of whether the incidence rate for each respective observation was statistically significanly increased (Inc.) comparable to the control group (-), or apparently decreased (Dec.).

Data were analyzed using Fisher's Exact Probability Test. $p<0.05$.

Individual values for these observations as well as those which were not statistically significantly different are presented elsewhere.

TABLE 13

Histopathologic Observations
Summary of Tumors in the Central Nervous System, Pituitary, Thyroid, and Adrenal Glands which were Statistically Significant in Male Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

	Dose ppm in H_2O	Cumulative Results
Number of rats necropsied during the time period indicated	0 ppm	80
	35 ppm	47
	100 ppm	48
	300 ppm	48
Nervous System		
Number of rats with only a focal or multifocal glial cell proliferation suggestive of early tumor in the central nervous system	0 ppm	0/80
	35 ppm	4/47**
	100 ppm	3/48
	300 ppm	7/48**
Number of rats with only a focal or or multifocal glial cell tumor (astrocytoma)/number of rats in the group	0 ppm	1/80
	35 ppm	8/47**
	100 ppm	19/48**
	300 ppm	23/48**
Number of rats with either a focal or multifocal glial cell proliferation suggestive of early tumor in the central nervous system and those with a focal or multifocal glial cell tumor (astrocytoma)/number of rats in the group	0 ppm	1/80
	35 ppm	12/47**
	100 ppm	22/48**
	300 ppm	30/48**
Pituitary Gland		
Number of rats with a pituitary tumor (adenoma or carcinoma)/number of rats in the group	0 ppm	24/80
	35 ppm	6/47[d]
	100 ppm	16/48
	300 ppm	5/48[d]
Thyroid Gland		
Number of rats with a C-cell tumor (adenoma or carcinoma)/number of rats in the group	0 ppm	15/80
	35 ppm	4/47
	100 ppm	2/48[d]
Adrenal Gland		
Number of rats with a pheochromocytoma (benign or malignant)/number of rats in the group	0 ppm	39/80
	35 ppm	21/47
	300 ppm	5/48[d]

TABLE 13 (Continued)

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*Source: Quast, et al. 1980.

**Statistically significant increase from control when analyzed using Fisher's Exact Probability Test, $p < 0.05$. Individual values for these observations as well as those which were not statistically significantly are presented elsewhere.

[d] Apparent decrease from controls, not corrected for early mortality.

the thoracic spinal cord. In general, the changes of a proliferative type in the cerebral cortex sections were most frequently observed in the section obtained from the middle of the cerebral hemisphere.

The endocrine gland tumors involving the pituitary, thyroid, and adrenals were all observed with significantly lower frequency in the 300 ppm group than in the control groups. In addition, the pituitary gland tumors in the 35 ppm group were also significantly decreased.

Histopathologic observations of tumors in the tongue, stomach, and pancreas which were observed to be statistically significant in treated male rats are summarized in Table 14. There was a statistically significantly increased incidence of squamous cell tumors of the tongue in the 300 ppm group. In the nonglandular portion of the stomach there was a statistically significant increase in the number of rats with a squamous epithelial tumor in the 100 and 300 ppm groups. As was noted on gross examination, there were many rats with multiple papillomas present in this region of the stomach. Upon microscopic examination of these stomach tumors some were found to be papillomas only, others were carcinomas only, and yet other rats had both papillomas and carcinomas.

Stages of the lesion progressed from hyperplasia and hyperkeratosis, to papilloma, and ultimately, carcinoma (papillary and ulcerating) formation, with some overlap in the sequence of lesion development. Tumors were not found in the stomach in the absence of either gross or histopathologic changes characterized by hyperplasia and hyperkeratosis and mixed with other degenerative and

TABLE 14

Histopathologic Observations
Summary of Tumors in the Tongue, Stomach, and Pancreas which were Statistically Significant in Male Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

	Dose ppm in H_2O	Cumulative Results
Number of rats necropsied during the the time period indicated	0 ppm	80
	35 ppm	47
	100 ppm	48
	300 ppm	48
Tongue		
Number of rats with a tumor of the squamous epithelium (papilloma or carcinoma)/number of rats in the group	0 ppm	1/80
	35 ppm	2/47
	100 ppm	4/48
	300 ppm	5/48**
Stomach - Nonglandular Portion[a]		
Rats with only a squamous cell papilloma	0 ppm	0/0/80
	35 ppm	2/2/47
	100 ppm	16/13/48**
	300 ppm	19/14/48**
Rats with only a squamous cell carcinoma	0 ppm	0/0/80
	35 ppm	0/0/47
	100 ppm	8/6/48**
	300 ppm	23/14/48**
Rats with both a squamous cell papilloma and a squamous cell carinoma in the same rat	0 ppm	0/0/80
	35 ppm	0/0/47
	100 ppm	10/4/48**
	300 ppm	32/11/48**
Rats with either a squamous cell papilloma, a squamous cell carcinoma or both tumor types present (total number of rats with a tumor in the nonglandular portion regardless of type)	0 ppm	0/0/80
	35 ppm	2/2/47
	100 ppm	34/23/48**
	300 ppm	74/39/48**
Pancreas - Acinar Portion[a]		
Pancreatic acinar adenoma (exocrine)	0 ppm	13/13/80
	35 ppm	4/4/47
	100 ppm	8/8/48
	300 ppm	1/1/48[d]

TABLE 14 (Continued)

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*Source: Quast, et al. 1980.

**Statistically significant increase from control when analyzed using Fisher's Exact Probability Test. $p < 0.05$.

[a] Data listed as number of this type of tumor/number of rats bearing this type of tumor/number of rats in the group. Individual values for these observations as well as those which were not statistically significantly different are presented elsewhere.

[d] Apparent decrease from control, not corrected for early mortality.

reactive changes. These observations were dose related in severity at the 100 and 300 ppm groups. There were greater numbers of rats with a carcinoma in the stomach at the highest dose level (Table 14), and they also showed a decreased latency period compared to the lower dose groups. The carcinomas which were present in the nonglandular stomach were predominantly papillary in type with only a small proportion of the rats with a carcinoma having the ulcerating type. Only a single ulcerating carcinoma of the nonglandular stomach invaded through the wall of the stomach and extended locally into the mesentery. Pancreatic exocrine adenomas were significantly decreased in the 300 ppm group and may partially be due to the earlier mortality of these rats.

Histopathologic observations of tumors in the ear canal gland (Zymbal's gland) which were statistically significant in treated rats and tumors in the subcutaneous region, mammary region, and pinna of the ear which were not statistically significant are summarized in Table 15. The incidence of Zymbal's gland tumors was statistically significantly increased only at the 300 ppm level when compared with the respective control group. The tumors in the subcutaneous tissue, mammary region, and pinna of the ear were not significantly different in treated and control rats and were summarized in this table for comparative purposes with the female rats.

Evaluation of the various tumor types present in the large intestine of treated male rats does not indicate a statistically significant increase in the incidence of any individual tumor type when the tumors were evaluated collectively without regard to cell

TABLE 15

Histopathologic Observations
Summary of Tumors in the Ear Canal, Subcutaneous Tissue, Mammary Gland, and Pinna of the Ear which were Statistically Significant in Male Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

	Dose ppm in H_2O	Cumulative Results
Number of rats necropsied during the time period indicated	0 ppm	80
	35 ppm	47
	100 ppm	48
	300 ppm	48
Ear Canal Gland (Zymbal's Gland)[a]		
Number of rats with a Zymbal's gland tumor (carcinoma)	0 ppm	3/3/80
	35 ppm	4/4/47
	100 ppm	3/3/48
	300 ppm	16/16/48**
Subcutaneous, Mammary, and Pinna of the Ear[a,b]		
Rats with a tumor in the subcutaneous region, mammary gland region, and pinna of the ear	0 ppm	21/19/80
	35 ppm	8/7/47
	100 ppm	13/13/48
	300 ppm	11/10/48

*Source: Quast, et al. 1980.

**Statistically significant increase from control when analyzed using Fisher's Exact Probability Test. $p < 0.05$.

[a] Data listed as number of this type of tumor/number of rats bearing this type of tumor/number of rats in the group. Individual values for these observations as well as those which were not statistically significantly different are presented elsewhere.

[b] No statistically significant differences were noted in this group of tumors.

type of origin. The combined number of small intestine tumors of epithelial type (carcinoma of glandular portion of stomach or duodenal junction and the small intestine) in the various groups was as follows: Control - 3/80; 35 ppm - 7/47; 100 ppm - 2/48; and 300 ppm - 8/48. The values were statistically significant in the 35 and 300 ppm groups when compared to controls. The total number of tumors, regardless of cell type of origin, in the glandular stomach or duodenal junction, small intestine, and large intestine of male rats was as follows: Control - 5/80; 35 ppm - 7/47; 100 ppm - 6/48; and 300 ppm - 9/48.

The necropsy findings and subsequent histopathologic examination of tissues of female rats revealed a variety of pathologic alterations which were considered treatment-related, and they were observed to occur with greater or lesser frequency than in the respective control group of rats. The frequency of microscopic findings of nontumorous changes was generally decreased in most organs at the higher dose levels, and was most probably because of the early mortality and the less severe degree of chronic renal disease noted in these rats. Tissues in female rats from the higher dose levels which were less frequently affected with nontumorous pathologic alterations were mammary gland, uterus, kidneys, pancreas, liver, adrenal glands, parathyroid glands, cardiovascular system, nervous system, and adipose tissue. An increased incidence of splenic extramedullary hematopoiesis secondary to hemorrhage associated with ulcerating tumors and increased hepatic atrophy as a result of the decreased nutritional state was observed in the 300 ppm group.

Organ systems in female rats showing a significantly increased incidence of nontumorous microscopic changes that were interpreted to be primary effects of ingesting water containing acrylonitrile were found in the nonglandular gastric mucosa and the CNS. In the stomach these changes were characterized by hyperplasia and hyperkeratosis in the nonglandular gastric mucosa and were observed to be significantly increased in the 100 and 300 ppm groups. In the brain of the 35 and 100 ppm groups of female rats there was a significantly increased incidence of focal gliosis and perivascular cuffing observed.

Gross pathologic observations of tumorous changes which were observed to be statistically significant in treated female rats are presented in Table 16. Based upon the gross observations, a significantly increased tumor incidence was observed in the ear canal gland (Zymbal's gland) at all levels, tongue at 300 ppm, stomach at 100 and 300 ppm, small intestine at 100 ppm, and brain at 300 ppm. A significant decrease in the tumor incidence of uterine endometrium was observed at 100 and 300 ppm and in the pituitary gland at all dose levels of acrylonitrile.

Histopathologic observations of tumors in the CNS, pituitary, thyroid, and adrenal glands which were statistically significant in treated female rats are presented in Table 17. A significantly increased incidence of a CNS tumor, characterized as an astrocytoma, was observed in rats at all dose levels. In addition, a significantly increased incidence of a focal or multifocal glial cell proliferation suggestive of an early tumor of the same cell type was observed in the 300 ppm group. The incidence of the CNS tumor

TABLE 16

Gross Observations of Tumorous Changes which were Statistically Significant in Female Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

Observation	Dose Level (ppm)		
	35	100	300
Integument and Subcutaneous Tissue			
Subcutaneous tumor - ear canal (Zymbal's gland)	Inc.	Inc.	Inc.
Tongue			
Tumor or tumor - like proliferation of the tongue	-	-	Inc.
Uterus			
Endometrial polyp(s)	-	Dec.	Dec.
Gastrointestinal Tract			
Gastric tumor - nonglandular region, focal papilloma ≤ 2 in tumor	-	Inc.	Inc.
Gastric tumor - nonglandular region, focal papilloma > 2 in tumor	-	-	Inc.
Gastric tumor - total number of rats with a primary tumor involving any part of the stomach	-	Inc.	Inc.
Small intestine - tumor(s) or diverticulum	-	Inc.	-
Nervous System			
Pituitary enlarged, suggestive of a tumor	Dec.	Dec.	Dec.
Brain - focal changes in consistency or color suggestive of primary tumor	-	-	Inc.

*Source: Quast, et al. 1980.

Results are listed on the basis of whether the incidence rate for each respective observation was statistically significantly increased (Inc.) comparable to the control group (-), or apparently decreased (Dec.).

Data were analyzed using Fisher's Exact Probability Test. $p < 0.05$.

Individual values for these observations as well as those which were not statistically significantly different are presented elsewhere.

TABLE 17

Histopathologic Observations
Summary of Tumors in the Central Nervous System, Pituitary, Thyroid, and Adrenal Glands which were Statistically Significant in Female Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

	Dose ppm in H_2O	Cumulative Results
Number of rats necropsied during the time period indicated	0 ppm	80
	35 ppm	48
	100 ppm	48
	300 ppm	48
Nervous System		
Number of rats with only a focal or multifocal glial cell proliferation suggestive of early tumor in the central nervous system	0 ppm	0/80
	0 ppm	3/48
	100 ppm	3/48
	300 ppm	7/48**
Number of rats with only a focal or or multifocal glial cell tumor (astrocytoma)/number of rats in the group	0 ppm	1/80
	35 ppm	18/48**
	100 ppm	22/48**
	300 ppm	24/48**
Number of rats with either a focal or multifocal glial cell proliferation suggestive of early tumor in the central nervous system and those with a focal or multifocal glial cell tumor (astrocytoma)/number of rats in the group	0 ppm	1/80
	35 ppm	21/48**
	100 ppm	25/48**
	300 ppm	31/48**
Pituitary Gland		
Number of rats with a pituitary tumor (adenoma or carcinoma)/number of rats in the group	0 ppm	44/80
	35 ppm	13/48[d]
	100 ppm	12/48[d]
	300 ppm	1/48[d]
Thyroid Gland		
Number of rats with a C-cell tumor (adenoma or carcinoma)/number of rats in the group	0 ppm	22/80
	35 ppm	7/48
	100 ppm	4/48[d]
	300 ppm	1/48[d]
Adrenal Gland		
Number of rats with a pheochromocytoma (benign or malignant)/ number of rats in the group	0 ppm	17/80
	35 ppm	3/48
	100 ppm	1/48[d]
	300 ppm	0/48[d]

TABLE 17 (Continued)

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*Source: Quast, et al. 1980.

**Statistically significant increase from control when analyzed using Fisher's Exact Probability Test, $p < 0.05$. Individual values for these observations as well as those which were not statistically significantly are presented elsewhere.

[d] Apparent decrease from controls, not corrected for early mortality.

was higher in female rats (Table 17) than in male rats (see Table 13) in each of the treatment groups. This observation was not inconsistent with that anticipated in view of the higher level of exposure (mg acrylonitrile/kg/day) of females than males.

The endocrine gland tumors involving the pituitary, thyroid, and adrenal glands were all observed at significantly lower frequency in the 100 and 300 ppm groups, as well as in the pituitary gland in the 35 ppm group. The decreased incidence of pituitary tumors in all dose groups was anticipated based on the gross observations.

Histopathologic observations of tumors in the tongue, stomach, small intestine and ear canal gland which were observed to be statistically significant in treated female rats are presented in Table 18. All of these organ systems showed a significantly increased tumor incidence in the 300 ppm groups. In addition, tumors were significantly increased in the nonglandular portion of the stomach in the 100 ppm group and in the ear canal gland (Zymbal's gland) in the 35 and 100 ppm groups. These tumors were identical to those previously indicated in the male rats.

Tumors involving mammary glands, subcutaneous tissue, skin, and pinna of the ear which were statistically significant in treated female rats are summarized in Table 19. In the evaluation of the female mammary gland tumors it was noted that 10/48 rats in the 300 ppm group had only a malignant tumor present (excludes rats with a benign mammary tumor only, as well as those rats which had

TABLE 18

Histopathologic Observations
Summary of Tumors in the Tongue, Stomach, Small Intestine, and Ear Canal which were Statistically Significant in Female Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

	Dose ppm in H_2O	Cumulative Results
Number of rats necropsied during the the time period indicated	0 ppm	80
	35 ppm	48
	100 ppm	48
	300 ppm	48
Tongue		
Number of rats with a tumor of the quamous epithelium (papilloma or carcinoma)/number of rats in the group	0 ppm	0/80
	35 ppm	1/48
	100 ppm	2/48
	300 ppm	12/48**
Stomach - Nonglandular Portion[a]		
Rats with only a squamous cell papilloma	0 ppm	1/1/80
	35 ppm	1/1/48
	100 ppm	12/12/48**
	300 ppm	25/18/48**
Rats with only a squamous cell carcinoma	0 ppm	0/0/80
	35 ppm	0/0/48
	100 ppm	0/0/48**
	300 ppm	1/1/48**
Rats with both a squamous cell papilloma and a squamous cell carinoma in the same rat	0 ppm	0/0/80
	35 ppm	0/0/48
	100 ppm	0/0/48**
	300 ppm	30/11/48**
Rats with either a squamous cell papilloma, a squamous cell carcinoma or both tumor types present (total number of rats with a tumor in the nonglandular portion regardless of type)	0 ppm	1/1/80
	35 ppm	1/1/48
	100 ppm	12/12/48**
	300 ppm	56/30/48**
Small Intestine		
Mucinous cystadenocarcinoma of small intestine without metastasis (adenomatus diverticulum type)	0 ppm	0/0/80
	35 ppm	1/1/48
	100 ppm	4/4/48[c]
	300 ppm	4/4/48**

TABLE 18 (Continued)

	Dose ppm in H_2O	Cumulative Results
Ear Canal Gland (Zymbal's Gland)[a]		
Number of rats with a Zymbal's gland tumor (carcinoma)	0 ppm	1/1/80
	35 ppm	5/5/48**
	100 ppm	9/8/48**
	300 ppm	18/18/48**

*Source: Quast, et al. 1980.

**Statistically significant increase from control when analyzed using Fisher's Exact Probability Test. $p < 0.05$.

[a] Data listed as number of this type of tumor/number of rats bearing this type of tumor/number of rats in the group. Individual values for these observations as well as those which were not statistically significantly different are presented elsewhere.

[c] Data not statistically analyzed because fewer sections of small intestine were examined at this dose level.

TABLE 19

Summary of Tumors in the Mammary Gland, Subcutaneous Tissue, Skin, and Pinna of the Ear which were Statistically Significant in Female Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

	Dose ppm in H_2O	Cumulative Results
Number of rats necropsied during the time period indicated	0 ppm	80
	35 ppm	48
	100 ppm	48
	300 ppm	48
Mammary Gland[a]		
Number of rats with only a benign mammary gland tumor (fibroademona/adenofibroma or adenoma)	0 ppm	91/52/80
	35 ppm	96/35/48
	100 ppm	85/33/48
	300 ppm	48/22/48[d]
Number of rats with only a malignant mammary gland tumor (carcinoma with or without metastasis)	0 ppm	1/1/80
	35 ppm	2/1/48
	100 ppm	3/3/48
	300 ppm	11/10/48**
Number of rats with a benign and a malignant gland tumor in the same rat	0 ppm	15/5/80
	35 ppm	18/6/48
	100 ppm	25/6/48
	300 ppm	8/3/48
Number of rats with a mammary gland tumor (benign only, malignant only, and both benign and malignant)	0 ppm	107/58/80
	35 ppm	116/42/48**
	100 ppm	113/42/48**
	300 ppm	67/35/48
Subcutaneous, Skin, or Pinna of the Ear[a,b]		
Rats with a tumor in the subcutaneous region (other than mammary gland), skin, and pinna of the ear	0 ppm	6/6/80
	35 ppm	2/2/48
	100 ppm	3/3/48
	300 ppm	2/2/48

TABLE 19 (Continued)

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*Source: Quast, et al. 1980.

**Statistically significant increase from control when analyzed using Fisher's Exact Probability Test. $p<0.05$.

[a] Data listed as number of this type of tumor/number of rats bearing this type of tumor/number of rats in the group. Individual values for these observations as well as those which were not statistically significantly different are presented elsewhere.

[b] No statistically significant differences were noted in this group of tumors.

[d] Apparent decrease from control, not corrected for early mortality.

both a benign and a malignant mammary tumor). This increased incidence in the 300 ppm group was statistically significant when compared to controls.

From Table 19, if the number of rats observed in each of the groups bearing a malignant mammary gland tumor is totaled, whether it was the only mammary tumor present or was also present with a benign tumor, the following results are obtained: Control - 6/80; 35 ppm - 7/48; 100 ppm - 9/48; and at 300 ppm - 13/48. The incidence of the rats bearing a malignant mammary gland tumor (when combined in this fashion) was also statistically significantly increased at the 300 ppm level. The mammary tumor incidence in the 300 ppm group was significantly decreased if only those rats with a benign mammary tumor were considered. The total number of female rats with a mammary tumor present, regardless of type, was significantly increased in the 35 and 100 ppm groups, and not different in the 300 ppm group, when compared to controls. Even though more rats in the treated groups contained a malignant mammary gland tumor, and even though they occurred earlier when compared with the controls, there was no evidence of increased metastatic activity as an expression of their malignancy.

In general, the occurence of the benign and the malignant mammary tumors in the treated female rats showed a dose-related decrease in latency period with increasing concentrations of acrylonitrile in the water. Other tumors of nonmammary origin in the subcutaneous region of the skin and involving the pinna of the ear did not show a tumorigenic response in the female rats. It was interesting to note that male rats also did not show a tumorigenic effect in the subcutaneous tissue, pinna of the ear, and the mammary gland (see Table 15). Therefore, the oncogenic response of mammary tissue in females was biologically quite different than that observed in males. The findings in female rat mammary tissue suggest that the response of this hormonally sensitive organ may have been significantly modified by the presence of acrylonitrile in the water acting through altered responses of the various endocrine glands.

The tumors of the reproductive tract involving uterus, cervix, or vagina are summarized in Table 20. There was a statistically significant decreased incidence in the uterine endometrial polyp(s) at the 300 ppm level. There was no evidence for a significant increase in any tumor type seen in the female reproductive tract at any treatment level.

Evaluation of the tumor data for the large intestine of female rats reveals that no primary tumors were present in the control or any treated groups. In the small intestine there was the following combined total number of tumors without regard to cell type of origin: Control - 1/80; 35 ppm - 1/48; 100 ppm - 4/48; and at 300 ppm - 5/48. The incidence of this tumor was statistically increased only in the 300 ppm group.

The total number of primary tumors and the number of rats with a primary tumor found upon microscopic examination of tissues from male and female rats maintained for two years on drinking water containing acrylonitrile are presented in Table 21.

During the first 18 months of the study, the percent of male rats with a tumor was considerably increased in the 300 ppm group

TABLE 20

Histopathologic Observations
Summary of Tumors in the Reproductive System which were Statistically Significant in Female Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*

	Dose ppm in H_2O	Cumulative Results
Number of rats necropsied during the time period indicated	0 ppm	80
	35 ppm	48
	100 ppm	48
	300 ppm	48
Reproductive System		
Number of rats with a uterine carcinoma without metastasis/number of rats in the group	0 ppm	2/80
	35 ppm	0/48
	100 ppm	3/48
	300 ppm	1/48
Number of rats with a uterine carcinoma with metastasis/number of rats in the group	0 ppm	1/80
	35 ppm	0/48
	100 ppm	2/48
	300 ppm	0/48
Number of rats with a uterine carcinoma (with or without metastasis)/number of rats in the group	0 ppm	3/80
	35 ppm	0/48
	100 ppm	5/48
	300 ppm	1/48
Number of rats with a uterine sarcoma (leiomyosarcoma, stromal, or neurofibrosarcoma) without metastasis/number of rats in the group	0 ppm	3/80
	35 ppm	2/48
	100 ppm	3/48
	300 ppm	4/48
Number of rats with a uterine sarcoma (leiomyosarcoma or nuerofibrosarcoma) with metastasis/number of rats in the group	0 ppm	0/80
	35 ppm	1/48
	100 ppm	1/48
	300 ppm	2/48
Number of rats with a uterine sarcoma (leiomyosarcoma, stromal, or neurofibrosarcoma) with or without metastasis/number of rats in the group	0 ppm	3/80
	35 ppm	3/48
	100 ppm	4/48
	300 ppm	6/48

TABLE 20 (Continued)

	Dose ppm in H_2O	Cumulative Results
Number of rats with a uterine endometrial polyp[a]	0 ppm	25/24/80
	35 ppm	6/6/48
	100 ppm	3/3/48
	300 ppm	6/6/48[d]

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*Source: Quast, et al. 1980.

[a] Data listed as number of this type of tumor/number of rats bearing this type of tumor/number of rats in the group. Individual values for these observations as well as those which were not statistically significantly different are presented elsewhere.

[d] Apparent decrease from control, not corrected for early mortality.

TABLE 21

Total Number of Primary Tumors Found Upon Microscopic Examination of Tissues from Male and Female Rats Maintained for 2 Years on Drinking Water Containing Acrylonitrile*[a]

Dose Level and Time Period	Males	Females
Controls		
0 to 6 Months	0/1/1	0/0/0
7 to 12 Months	6/4/6	1/1/1
13 to 18 Months	39/18/23	18/10/11
19 to 24 Months	80/37/43	159/48/48
Terminal Kill	27/7/7	72/19/20
Cumulative	152/67/80	250/78/80
35 ppm		
0 to 6 Months	0/0/0	0/0/0
7 to 12 Months	2/2/2	2/1/1
13 to 18 Months	13/7/14	39/13/13
19 to 24 Months	52/23/26	131/29/30
Terminal Kill	17/5/5	19/4/4
Cumulative	84/37/47	191/47/48
100 ppm		
0 to 6 Months	1/1/1	0/0/0
7 to 12 Months	0/0/0	5/3/3
13 to 18 Months	35/15/16	78/20/20
19 to 24 Months	90/26/26	129/24/24
Terminal Kill	26/5/5	5/1/1
Cumulative	152/47/48	217/48/48
300 ppm		
0 to 6 Months	0/0/0	1/1/1
7 to 12 Months	4/2/4	30/13/13
13 to 18 Months	84/26/26	118/23/23
19 to 24 Months	90/18/18	68/11/11
Terminal Kill	0/0/0	0/0/0
Cumulative	178/46/48	217/48/48

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*Source: Quast, et al. 1980.

[a] Data listed as number of tumors/number of rats with tumors/number of rats dying during that time period.

when compared to the controls. The tumor incidence of male rats in the 35 ppm and the 100 ppm groups were comparable to the controls during this period. However, the number of tumors per male rat bearing a tumor during the first 18 months of the study was increased in rats of the 100 and 300 ppm groups compared to both the control and the 35 ppm groups.

In the female rats during the first 18 months of the study there was an increase in the percent of rats with a tumor and in the number of tumors per rat with a tumor at all treatment levels when compared to controls. The data indicate that female rats at all treatment levels showed a greater tumorigenic response and a shorter latency period for tumor development than did the males during the first 18 months of the study.

In conclusion, the development of tumors in various organ systems of male and female rats ingesting water containing acrylonitrile for two years has been demonstrated in this study.

In the intestinal tract of male and female rats, the total number of tumors in locations other than the nonglandular gastric mucosa was statistically significantly elevated only in the 300 ppm group. A carcinoma of the small intestine was the most frequently observed tumor in the male and female treated rats with an intestinal tumor. There were no tumors in the large intestine of female rats and those present in males did not show a statistically significantly increased incidence.

Tumors of endocrine glands involving the pituitary, thyroid, and adrenals were usually decreased in both male and female rats at all treatment levels. In addition, the pancreatic exocrine adenomas in males at the 300 ppm level and the uterine endometrial polyp in females at all treatment levels were also decreased in incidence.

In general, the rats ingesting the highest dose level of acrylonitrile showed the earliest onset and greatest number of tumors with a larger number of malignant tumors which infrequently metastasized. Female rats did exhibit a slightly greater toxic and tumorigenic response than males, and this was concluded to be a result of the higer dose of acrylonitrile (mg/kg/day) consumed by the females than the males.

Manifestations of toxicity and tumorigenicity were produced in this 2-year rat study using high dose levels of acrylonitrile in the drinking water. A lifetime study conducted in rats using dose levels of acrylonitrile in their drinking water which they no longer voluntarily reject would be most useful in placing some relevant perspective to the toxic and tumorigenic response observed in rats of this 2-year study. For assessing risk, additional data are needed for rats receiving lower levels of acrylonitrile in their drinking water.

It should be noted that Zymbal's gland tumors were also reported in rats during a 3-year reproduction study in rats (Beliles, et al. 1980; Murray, et al. 1976) (see Teratogenicity section).

In further support of the above data, a letter transmitted by the Manufacturing Chemists Association dated February 22, 1978 includes a summary of preliminary findings of a study by Dow Chemical U.S.A. indicating a higher incidence of brain tumors at 80 and 20 ppm in drinking water when compared to historic control data.

Maltoni, et al. (1977) have recently reported the results of long-term carcinogenicity bioassays of acrylonitrile, lasting more than 130 weeks. The monomer has been tested in Sprague-Dawley rats by inhalation (40, 20, 10, and 5 ppm, 4 hours daily, 5 times weekly for 52 weeks) and by ingestion (5 mg/kg body weight in olive oil by stomach tube, once daily, 3 times weekly for 52 weeks). A slight enhancement of the incidence of some tumors has been reported, i.e., mammary tumors, fore-stomach papillomas and acanthomas, skin carcinomas, and encephalic tumors, particularly gliomas.

It should be noted that only one dose was used in the ingestion studies, so that no-dose response relationship could be obtained. Data from the inhalation studies are presented on mammary tumors and Zymbal's gland carcinomas and on encephalic tumors (particularly gliomas), uterine carcinomas and others (Table 22).

As an additional note it should be pointed out that possible impurities found in the acrylonitrile used by various investigators might possibly affect the determination of carcinogenic effect. The role of these impurities has not yet been determined.

A recent preliminary epidemiological study from E. I. du Pont de Nemours and Company on its Camden, South Caroline textile fibers plant showed that persons exposed to acrylonitrile at the plant are at greater risk of developing cancer, as compared with company, national and regional experience (O'Berg, 1979). This preliminary retrospective study analyzes the cancer experience of the cohort of 1,343 workers who were exposed to acrylonitrile between 1950 and 1967. It considers no latency, 15-year latency and 20-year latency

TABLE 22

Results of Inhalation Study by Maltoni, et al. 1977.

GROUPS No.	TREATMENT		ANIMALS (Sprague-Dawley Rats, 12 weeks old at start)		Corrected number (a)	ANIMALS WITH TUMOURS														
						Mammary tumours												Zymbal gland carcinomas		
										Histotypes										
										Fibroadenomas and fibromas				Carcinomas						
	Dose	Length (weeks)	Sex	No. at start		No.	% (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)	Average latency time (weeks) (c)
I	40 ppm	52	♀	30	30	7	23.3	89.4	1.4	5	16.6	94.4	1.4	2	6.6	77.0	1.5	-	-	-
			♂	30	30	4	13.3	112.5	1.0	3	10.0	130.7	1.0	1	3.3	58.0	1.0	-	-	-
			♀ and ♂	60	60	11	18.3	97.8	1.3	8	13.3	106.0	1.2	3	5.0	70.7	1.3	-	-	-
II	20 ppm	52	♀	30	30	10	33.3	107.4	1.0	9	30.0	110.7	1.0	1	3.3	78.0	1.0	1	3.3	77
			♂	30	30	4	13.3	41.5	1.0	2	6.6	48.0	1.0	2	6.6	35.0	1.0	-	-	-
			♀ and ♂	60	60	14	23.3	88.6	1.0	11	18.3	99.3	1.0	3	5.0	49.3	1.0	1	1.6	77
III	10 ppm	52	♀	30	30	7	23.3	102.3	1.4	7	23.3	102.3	1.4	-	-	-	-	1	3.3	101.0
			♂	30	30	1	3.3	114.0	1.0	1	3.3	114.0	1.0	-	-	-	-	1	3.3	104.0
			♀ and ♂	60	60	8	13.3	103.7	1.4	8	13.3	103.7	1.4	-	-	-	-	2	3.3	102.5
IV	5 ppm	52	♀	30	30	10	33.3	92.2	1.2	6	20.0	93.0	1.3	4	13.3	91.0	1.0	-	-	-
			♂	30	30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			♀ and ♂	60	60	10	16.6	92.2	1.2	6	10.0	93.0	1.3	4	6.6	91.0	1.0	-	-	-
V	None (Controls)		♀	30	30	5	16.6	94.0	1.0	4	13.3	93.0	1.0	1	3.3	98.0	1.0	-	-	-
			♂	30	30	1	3.3	135.0	1.0	-	-	-	-	1	3.3	135.0	1.0	-	-	-
			♀ and ♂	60	60	6	10.0	100.8	1.0	4	6.6	93.0	1.0	2	3.3	116.5	1.0	-	-	-
Total				300	300															

(a) Alive animals after 2 weeks, when the first tumour (a mammary carcinoma) was observed.

(b) The percentages are referred to the corrected number.

(c) The latency time of mammary tumours is given as age; the latency time of the other tumours is given as period from the start of the experiment.

periods for cancer development. About 36 percent of the 1,343 employees are presently lost to follow-up.

In this study, mortality rates were analyzed for active employees and retirees, and cancer diagnoses and deaths for active employees were analyzed using company and national referent rates to determine expected numbers. The most sensitive analysis, using du Pont referent rates (correcting for the "healthy worker effect") and a 20-year induction for cancer (which narrows down the cohort to 470) indicated eight observed deaths compared with 4.0 expected. The du Pont Registry data revealed 16 cases of cancer compared to 5.8 expected. The difference was found to be highly significant (Tables 23 and 24).

The author of the study notes that the results presented are preliminary, and that additional follow-up of persons who quit or were laid off is required. In the cohort, the losses to follow-up represent a significant percentage (36 percent). About one-third of the losses have had short-term exposure (less than six months). The acrylonitrile exposure levels were only qualitatively reported (on the basis of the job and its potential for exposure) as 3 (lowest exposure), 2 (moderate exposure) or 1 (highest exposure). Times at each level were estimated for each cancer mortality. Excess cancer was observed when considering all sites; individual sites with excess cancer mortality were lung, large intestine, and possibly prostate (Tables 23 and 24). The excess cancer in the cohort is distributed among many anatomical sites although lung and intestinal cancer predominate. Significant excess overall cancer mortality cannot be entirely attributable to these primary sites.

TABLE 23

Observed and Expected Numbers of Cancer Deaths* for an Acrylonitrile Cohort with Six Months or Greater Exposure, Based on du Pont Company Rates for 1969-1975, 20-Year Latency**

	Male Wage			Male Salary	
	Observed	Expected	P-Value	Observed	Expected
All sites	7	3.4	0.06	1	0.6
Lung	4	1.3	0.04	0	0.2
Large Intestine	2	0.2	0.02	0	0.1
Prostate	1	0.1		0	.0

*Cancer Registry Entries (active employees only).

**Source: O'Berg, 1979.

TABLE 24

Observed and Expected Numbers of Cancer Cases* for a Cohort with Six Months or Greater Exposure, Based on du Pont Company Rates for 1969-1975,

20-Year Latency**

	Male Wage			Male Salary	
	Observed	Expected	P-Value	Observed	Expected
All sites	14	4.9	0.0006	2	0.9
Lung	5	1.3	0.011	1	0.2
Large Intestine	3	0.4	0.008	0	0.1
Prostate	1	0.3		0	0.1

*Cancer Registry Entries (active employees only).

**Source: Adapted from O'Berg, 19[illegible]9.

Because an excess of lung cancer occurs in this cohort, cigarette smoking must be considered as a possible agent or cofactor; smoking histories were not available for this interim report however (O'Berg, 1979). Another consideration should also be mentioned; the du Pont cohort had in common exposure to the following chemicals besides acrylonitrile: dimethylformamide, hydrogen peroxide, hydroxyanisole, methyl acrylate, phenylether-biphenyl mixture, sodium metabisulfite, sulfur dioxide, sulfuric acid, and titanium dioxide (O'Berg, 1977b). A tabulated list of all cancer cases appear in Table 25 (O'Berg, 1977a).

Monson analyzed the cancer mortality (and morbidity) experience of 355 white male United Rubber Workers Union members who had potential exposure to acrylonitrile in the polymerization recovery and laboratory areas of B.F. Goodrich plant #3, Akron, Ohio (Table 26) (43 FR 45762). The mortality experience of this cohort between January 1, 1940 and July 1, 1976 was compared to that of the U.S. general population. Person-years of follow-up were determined in 5-year age-time groupings, and expected numbers were calculated by multiplying these person-years by age-time-cause specific mortality rates for U.S. white males. The cancer registries for the four Akron area hospitals were reviewed between 1964 and 1974.

Determination was also made of any B]F] Goodrich employee who developed cancer between these years. In addition, persons who had cancer as the secondary cause of death on the death certificate were identified. Based on these data, Monson compared cancer morbidity rates in men who worked in departments with potential exposure to acrylonitrile with unexposed male workers (43 FR 45762).

TABLE 25

Cohort Cancer Cases and/or Deaths,* 1969-1975, Duration of Exposure**

Cancer Site	Date of First Exposure	Total Years of Exposure Rounded to Nearest Whole Year	Time at Severity		
			1	2	3
Lung	1950	26	18 yr.	8 yr.	
Lung	1950	20			20 yr.
Lung	1950	7	5 yr. 1 mo.	1 yr. 4 mo.	2 mo.
Lung	1950	4	1 yr. 2 mo.	1 yr. 2 mo.	2 yr. 1 mo.
Lung	1952	5	5 yr. 1 mo.		
Lung	1952	4	1 yr. 2 mo.		3 yr. 4 mo.
Large Intestine	1951	13			13 yr. 1 mo.
Large Intestine	1951	5	5 yr.		6 mo.
Large Intestine	1952	5	5 yr.		
Prostate	1950	14			13 yr. 9 mo.
Prostate	1952	5	5 yr. 3 mo.		
Lymphosarcoma	1951	1			4 mo.
Hodgkins	1951	13			12 yr. 9 mo.
Penis	1952	12		8 mo.	11 yr.
Thyroid	1952	14	2 yr. 8 mo.	1 yr. 8 mo.	10 yr.
Nasopharynx	1950	7			7 yr. 4 mo.
Bladder	1950	3	3 yr. 1 mo.		
Pancreas	1952	6	6 yr.		

*20-year latent period assumed.
**Source: O'Berg, 1979.

TABLE 26

Observed and Expected Deaths for 355 White Male Union Members Who Ever Worked in Department 5570 - 5579*

ICD No.**	Cause of Death	Observed	Expected	SMR***
	All causes	64	83.1	77
140-205	Malignant neoplasms	20	15.6	128
150-159	Digestive	4	4.6	88
153	Large intestine	1	1.3	74
160-164	Respiratory	9	5.2	175
177-181	Genitourinary	2	1.7	117
200-205	Lymphatic & hematopoietic	3	1.6	186
-	Residual cancer	2	2.2	94
330-334	Cerebrovascular disease	5	5.1	97
400-486	Circulatory disease	22	37.5	59
470-527	Respiratory disease	5	4.3	117
530-581	Digestive disease	2	4.5	44
590-637	Genitourinary disease	1	1.3	77
800-999	External causes	5	8.8	57
-	Residual	4	10.5	38

*Source: 43 FR 45762.

**International Classification of Diseases. 7th Revision.

***Standardized Mortality Ratio: 100 x observed/expected.

According to this study Monson reported that among the male cohort who had some exposure to acrylonitrile as well as other chemical exposure in the cohort (such as butadrene), the most significant finding was an excess of lung cancer (9 observed, 5.2 expected) (43 FR 45762). Among lymphatic and hematopoietic cancers there were 3 deaths where 1.6 were expected. Monson reported that there were no excess deaths from cancer of the large intestine. He also reported that the excess of mortality due to cancer from all sites and of the lung was seen primarily in men who started working after 1939 and died after 1959 (Table 27) (43 FR 45762). He reported that there were six men identified through the Akron tumor registries as having cancer; none of these men were known to be dead as of July 1, 1976. The sites of the cancers of these six men were; large intestine (1), kidney (2), bladder (1), skin (1), and lymphoma (1). He concluded that an excess of cancer as measured by mortality or morbidity occurred among men who had exposure to acrylonitrile. The excess was spread over a number of sites but was greatest for lung cancer. He indicated that he is unable to determine whether this excess represents a casual association with work in those departments in which potential exposure to acrylonitrile may occur. He also indicated that the study is confounded by the fact that most of the acrylonitrile exposed workers developing cancer had worked in other departments where they were potentially exposed to other chemicals. Finally, Monson concluded that although proof does not exist that the current levels of acrylonitrile and other chemical exposures (such as butadien) are harmful, it would be prudent to reduce further exposure to the chemical

TABLE 27

Observed and Expected Deaths from all Cancers and Lung Cancer According to Selected Characteristics*

Characteristic	Category (years)	All Cancers		Lung Cancer	
		Obs.	Exp.	Obs.	Exp.
Age started working**	35	5	4.9	2	1.2
	35-44	5	4.7	1	1.8
	45	10	6.0	6	1.8
Year started working	1940	0	0.6	0	0.2
	1940-49	12	7.9	3	2.3
	1950	8	7.1	6	2.3
Age at death	65	11	11.1	5	3.5
	65	9	4.5	4	1.3
Year of death	1960	3	2.6	0	0.6
	1960-69	9	6.2	4	1.9
	1970	8	6.8	5	2.3

*Source: 43 FR 45762.

**Age and year refer to entrance into 5570-5579.

(43 FR 45762). No quantitative exposures of acrylonitrile are listed in the report. Monson (43 FR 45762) notes that his data at Goodrich conflicts with O'Berg's (1979) du Pont study in which an excess of intestinal cancer was observed. Aside from differences in other chemical exposures suffered by the two cohorts, Monson did not assume a 20 year latency period (providing greater sensitivity) (43 FR 45762), while O'Berg (1979) did.

CRITERION FORMULATION

Existing Guidelines and Standards

The existing standards for acrylonitrile in various countries and various years appear in Table 28.

It is evident that at this time, the Russian standard is substantially less (two orders of magnitude) than the American and west European standards. The work of Scupakas (1968) indicates, however, that the standard may be exceeded significantly. The study of Orusev and Popovski (1973) of a Yugoslavian acrylic fiber plant indicated that their in-plant concentrations of acrylonitrile begin to approach the threshold limit value (TLV) in the U.S. Other investigators have noted that the air standards are often exceeded (Schwanecke, 1966; Thiede and Franzen, 1965; Babanov, 1960), although it is unlikely that higher concentrations occur throughout the day.

Almost 20 years ago, it was advocated by Elkins (1959) in the U.S. that the maximum allowable concentration (MAC) be reduced to 10 ppm (corresponding to that of HCN). According to Babanov (1960) an acute danger exists even from 0.85 to 6.1 mg/m^3 (0.4 to 2.8 ppm) in working areas.

In January, 1978, the Occupational Safety and Health Administration (OSHA) announced an emergency temporary standard to reduce sharply worker exposure to acrylonitrile. OSHA director, Dr. Eula Bingham, directed that, effective immediately, employee exposure to acrylonitrile must be reduced to 2 ppm averaged over an 8-hour period [time-weighted average (TWA)]. Dr. Bingham noted that the Emergency Temporary Standard was necessary because of data from

TABLE 28

Standards for Arcylonitrile Air Exposure Levels in Various Countries (between 1970-1974)

Year	Country	Air ppm	Standard mg/m^3	Kind of Standard	Reference
1970	USSR	0.2	0.435	MAC ("Hygenic goal")	Grahl, 1970; Schwanecke, 1966; Babanov, 1960; Pokrokovsky, 1951; Thiede and Franzen, 1965
1970	Federal Republic of Germany	20.0	43.5	MAK	Grahl, 1970; Thiede and Franzen, 1965; Lefaux, 1966
1970	England	20.0	43.5	MAC	Grahl, 1970; Thiede and Franzen, 1965; Lefaux, 1966
1974	U.S.	20.0	43.5	TLV	ACGIH, 1974; Grahl, 1970; Mallette, 1943; Dudley and Neal, 1942

studies of workers previously exposed to acrylonitrile and laboratory tests, both of which established "exposure to acrylonitrile poses a potential carcinogenic risk to humans." While OSHA's position is that there is no way to determine a safe level of exposure to a carcinogen, in this case "a level was chosen to immediately minimize the hazard to the greatest extent possible within the confines of feasibility" (Anonymous, 1978a).

Current Levels of Exposure

Indices of exposure, apart from very unspecific symptoms (such as spirographic examination of the lung) in the case of chronic exposure (Possner, 1965), include the determination of increased blood SCN^- level (Mallette, 1943; Wilson, et al. 1948; Lawton, et al. 1943) and elevated urinary SCN^- level (Mallette, 1943; Sax, 1957; Elkins, 1959; Lawton, et al. 1943).

It must be recognized that smoking presents a problem in ascertainment of occupational and other exposure because of the presence of nitriles in cigarette smoke. Thus, smokers may have a blood level of approximately 3 mg percent SCN^- in blood; the urinary SCN^- level of heavy smokers may normally reach 9 mg KSCN/l in contrast to a normal urinary level for nonsmokers of 0.2 mg/l and for occasional smokers a normal urinary level of 1.2 mg KSCN/l (Elkins, 1959). Consequently, in testing for occupational or other exposure, if it is not known whether a person is a smoker, values of urinary KSCN __ 10 mg/l cannot be considered to result from occupational exposure. Sax (1957) suggests that it is advisable for the purposes of screening for exposure to have liver function tests if urinary analysis proves to be negative. In addition, another suggested method of screening is that of the spectrophotometric determination of cyanomethemoglobin in blood (Magos, 1962).

The existing occupational standards have already been mentioned. It has also been noted that these standards are often exceeded in the USSR. The production of significant amounts of acrylonitrile and HCN from thermal decomposition of polyacrylonitrile products has already been noted. For example, from the overheating of 1 kg of a polyacrylonitrile plastic, about 15 g of HCN can be formed. Thus, the amount of HCN formed in a 30 m^3 room from 100 to 200 g of polyacrylonitrile fibers corresponds to 10 to 15 times the MAC values (Schwanecke, 1966; Thiede and Franzen, 1965; Mallette, 1943), and this underlines a special hazard of polyacrylonitrile plants. The possible synergism of acrylonitrile and HCN has already been alluded to.

There are few data on monitoring of ambient air and drinking water levels of acrylonitrile. A notable exception is the analysis of in-plant air emission from a propylene-based acrylonitrile manufacturing plant by Hughes and Horn (1977). This lack of data prevents us from predicting most actual exposures of the public except for certain groups at high risk such as occupational workers. At the present Emergency Air Standard, 2 ppm of acrylonitrile = 4.35 mg/m^3/day, the acrylonitrile intake of a worker at threshold level = 0.90 (4.35 mg/m^3) (20 m^3/day) = 78.3 mg/day, where 0.90 is the average retention of acrylonitrile (Young, et al. 1977). Thus, depending on the half-life of acrylonitrile, a substantial body burden in occupationally exposed individuals can result.

As indicated in the Exposure section, some additional environmental monitoring data is becoming available (Midwest Research Institute, 1977, 1978). However, to date this information is preliminary in nature and conclusions on possible human exposure cannot be drawn.

Other groups at risk are listed in the next section. Due to a lack of data, it is impossible to calculate the actual intakes of acrylonitrile for these groups.

Special Groups at Risk

Shown in Tables 29 and 30 are various groups at varying degrees of risk to acrylonitrile exposure with attached references wherever feasible. It should be recalled that NIOSH has estimated that at least 125,000 individuals are exposed occupationally (NIOSH, 1977).

Basis and Derivation of Criterion

The animal carcinogenicity studies of Quast, et al. (1980) and Maltoni, et al. (1977) and the epidemiological studies of O'Berg (1979) and Monson (1977) were considered to be the most pertinent data for the determination of a water quality criterion for the protection of human health. Although the epidemiological studies showed excesses of various cancers in man, neither study had quantitative exposure data of the workers to acrylonitrile and hence could not be utilized for calculation of a safe level. The criterion was therefore developed from the animal carcinogenicity data by utilizing a linearized multistage model as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice, which announced the availability of this document.

TABLE 29

Occupational Exposure to Acrylonitrile

Occupational	
1. Plastic	(NIOSH, 1977)
Acrylonitrile Manufacturers	(NIOSH, 1977)
Polymer Manufacturers	(NIOSH, 1977)
Polymer Molders	(Scupakas, 1968)
Polymer Combustion Workers	(Rumberg, 1971; Duvall and Rubey, 1973)
Furniture Makers	(Vol'skii, et al. 1973)
2. Fabrics	(Rapaport, et al. 1974)
Fiber Manufacturers	(Orusev and Popovski, 1973; Valic and Zuskin, 1977)
Clothing Sewers	(Fedorchuk, 1973)
3. Biological Product Manufacturing	
Dental Polymer Manufacturers	(Crapper, et al. 1978)
Contact Lens Fabricators	(Stoy, et al. 1976)
Blood Filter Fabricators	(Lindsay, et al. 1977)
4. Water Treatment and Manufacturers	(Sato, et al. 1977)
5. Pesticide and Fumigant	
Manufacturers	(Radimer, et al. 1974)
Sprayers	(Radimer, et al. 1974)
Farmers	(Radimer, et al. 1974)

TABLE 30

Nonoccupational Exposure to Acrylonitrile

1. Accidental	
Exposure to liquid from transportational spill	(Hardy, et al. 1972)
Combustion and fire (firemen and domestic personnel)	(Duvall and Rubey, 1973; Michal, 1976; Hilado, et al. 1977)
Ingestion of contaminated water or food	(Chudy and Crosby, 1978; Vettorazzi, 1977)
Respirations of Contaminated Air (environmental exposure to acrylonitrile or polyacrylonitrile plants)	
2. Non-accidental	
Cigarette smokers	(Izard and Testa, 1968)
Wearers of acrylic dentures	(Crapper, et al. 1978)
Wearers of acrylic underwear, diapers, and sanitary napkins	(Rapoport, et al. 1974; Harada and Shimodi, 1976)
Ingestion of food wrapped in polyacrylonitrile wrapping	(Federal Register, 1974, 1975, 1976)
Exposure to acrylonitrile vapors from polyacrylonitrile furniture	(Vol'skii, et al. 1973)

The rat carcinogenicity studies, in general, showed a tumorigenic response to acrylonitrile whether exposure was by ingestion or inhalation. These data support the findings of the epidemiological studies.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Acrylonitrile is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of acrylonitrile in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of acrylonitrile corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the following table.

Exposure Assumptions per day	Risk Levels Corresponding Criteria (1)		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 grams of fish and shellfish (2)	0.006 µg/l	0.058 µg/l	0.58 µg/l
Consumption of fish and shellfish only.	0.065 µg/l	0.65 µg/l	6.5 µg/l

(1) Calculated by applying a linearized multistage model as previously mentioned to the animal bioassay data presented in the Appendix. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Nine percent of the acrylonitrile exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 30-fold. The remaining 91 percent of the acrylonitrile exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of acrylonitrile (1) occurring from the consumption of both drinking water and aquatic life grown in water containing the corresponding acrylonitrile concentrations and, (2) occurring solely from the consumption of aquatic life grown in the waters containing the corresponding acrylonitrile concentrations.

Because data indicating other sources of exposure and the contribution to total body burden are inadequate for quantitative use, the criterion reflects the increment to risks associated with ambient water exposure only.

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APPENDIX

Summary and Conclusions Regarding the Carcinogenicity of Acrylonitrile (AN)*

Acrylonitrile has a molecular structure (CH_2=CH-CN) which resembles that of vinyl chloride (CH_2=CH-Cl), a chemical known to cause animal and human cancer. Principally, it is used as an intermediate in the manufacture of a wide variety of acrylic fibers, plastics, and in synthetic rubber.

Acrylonitrile is mutagenic in the Ames _Salmonella_ _typhimurium_ strains TA1535, TA1538, and TA1978 in the presence of mammalian metabolic activation which indicates both base-pair substitution and frameshift mechanisms of action. It is also reported weakly positive in _Drosophila_.

There is strong preliminary evidence that acrylonitrile is likely to be a human carcinogen. This conclusion is based on the following studies: (1) one final and one preliminary report by the Dow Chemical Co. bioassay of acrylonitrile given in drinking water to Sprague-Dawley rats; (2) carcinogenicity of acrylonitrile in Sprague-Dawley rats by Maltoni, administered via inhalation; and (3) an epidemiologic study by E.I. du Pont de Nemours and Co., Inc. indicating an excess of lung and colon cancer incidence among active employees in the company working with acrylonitrile as compared to that of the national experience. In these three studies, acrylonitrile has induced excess tumor incidence of the central nervous system as compared to the controls.

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*This summary has been prepared and approved by the Carcinogens Assessment Group of U.S. EPA on June 15, 1979.

In summary, carcinogenic responses have been induced in Sprague-Dawley rats and humans. These results, together with the positive mutagenic response, constitute clear evidence that acrylonitrile is likely to be a human carcinogen.

The water quality criterion for acrylonitrile is based on astrocytoma induction of the central nervous system in female Sprague-Dawley rats given acrylonitrile via the drinking water, as observed and reported by the Dow Chemical Co. (Quast, et al. 1980). It is concluded that the water concentration of acrylonitrile should be less than 0.58 µg/l in order to keep the lifetime cancer risk below 10^{-5}.

Summary of Pertinent Data

The water quality criterion for acrylonitrile is derived from the induction of astrocytomas observed in the central nervous system of female Sprague-Dawley rats given acrylonitrile in drinking water (Quast, et al. 1980). The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)[a]
0	0/80
4.36	17/48
10.76	22/48
24.97	24/48

le = 738 days

Le = 738 days

L = 738 days

w = 0.314 kg

R = 30 l/kg

With these parameters the carcinogenic potency factor for humans, q_1^*, is 0.552 $(mg/kg/day)^{-1}$. The resulting water concentration of acrylonitrile calculated to keep the individual risk below 10^{-5} is 0.58 µg/l.

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[a] The incidence at the highest dose group was not used in the linearized multistage extrapolation because of lack of fit. See the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document for a complete discussion on the lack of fit of data to the linearized multistage model.